

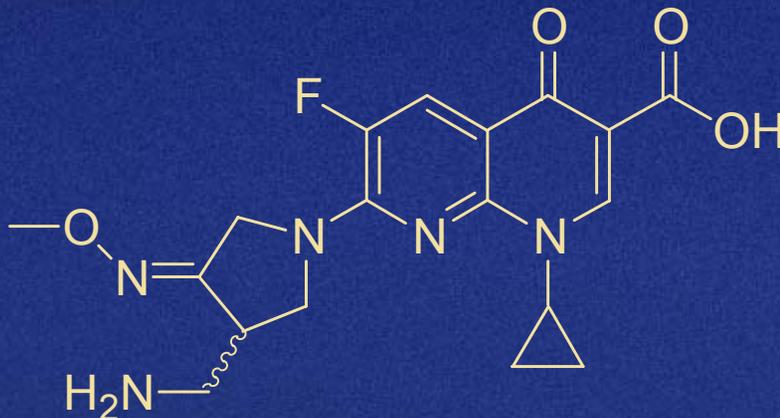
Factive[®] (gemifloxacin)
NDA #21-158

FDA Advisory Committee Meeting
March 4, 2003

Gemifloxacin

A Potent Dual Targeting Fluoroquinolone

- Potent Gram-positive activity
(MIC₉₀ *S.pneumoniae* 0.03 µg/mL)
- Effective against quinolone-resistant respiratory pathogens



Pharmacokinetics

- Rapidly absorbed, $T_{max} = 0.5-2$ h
- 70% oral bioavailability
- $T_{1/2} = 8$ hours for once daily dosing
- Plasma protein binding = 55-65%
- No cytochrome P450 interaction
- Both renal and biliary clearance

Gemifloxacin Regulatory History

Oct 1997 — INDs filed

Dec 1999 — NDA filed (CAP, AECEB, ABS, uUTI, cUTI)

Dec 2000 — Non approvable letter

Apr 2000 — Additional studies at FDA request (Study 344)

Oct 2002 — NDA resubmitted (CAP, AECEB)

Mar 2003 — FDA Advisory Committee Meeting

Gemifloxacin Clinical History

- Clinical trial program **9931**
- Oral 320 mg dose in phase II/III trials **6775**

Indications/Dose/Treatment Durations

- Indications
 - Acute Exacerbation of Chronic Bronchitis (AECB)
 - Community Acquired Pneumonia (CAP)
- Treatment dose
 - 320 mg
 - Once daily by mouth
- Treatment durations
 - 5 days for AECB
 - 7 days for CAP

Agenda

- Introduction

Gary Patou, MD

President, GeneSoft Pharmaceuticals

- Unmet Medical Need

Donald E. Low, MD

*Professor, Microbiology and Medicine,
University of Toronto*

- Efficacy

Lionel A. Mandell, MD

*Professor of Medicine, Chief of Infectious
Diseases, McMaster University*

- Safety

Gary Patou, MD

President, GeneSoft Pharmaceuticals

Neil H. Shear, MD

*Professor and Chief Dermatology, Director,
Drug Safety Research Group, University of Toronto*

- Benefit/Risk and Risk Management

Gary Patou, MD

President, GeneSoft Pharmaceuticals

Additional Experts

- **Project Medical Director**
 - **Wayne M. Dankner, MD**
Sr. Medical Director, Parexel; Assoc. Professor, Duke University Medical Center
- **Dermatology**
 - **James J. Leyden, MD**
Professor Emeritus, Department of Dermatology, University of Pennsylvania
 - **Mark H. Lowitt, MD**
Vice Chairman, Department of Dermatology, University of Maryland
- **Dermatopathology**
 - **Wedad Hanna, MD, FRCPC**
Chief, Dept. of Pathology, Sunnybrook and Women's College Health Sciences Center
 - **Judit Zubovits, MD, FRCPC**
Dept. of Anatomic Pathology, Sunnybrook and Women's College Health Sciences Center
- **Immunology**
 - **Werner Pichler, MD**
Head, Division of Allergy, University of Bern, Switzerland
- **Hepatology**
 - **James Lewis, MD**
Professor of Medicine, Director of Hepatology, Georgetown University
 - **Paul Watkins, MD**
Professor of Medicine, Director, General Clinical Research Center, University of N. Carolina

Additional Experts

- **Cardiology**

- **Jean T. Barbey, MD**

- Assistant Professor, Depts of Pharmacology and Medicine, Georgetown University Hospital*

- **Microbiology**

- **Steve Brown, PhD**

- Director, The Clinical Microbiology Institute, Wilsonville, Oregon*

- **Michael Jacobs, MD, PhD**

- Director, Medical Microbiology, University Hospitals of Cleveland*

- **Keith Klugman, MD**

- Professor of Medicine, Division of Infectious Diseases, Emory University*

- **Toxicology**

- **John Connelly, PhD**

- Former Director of Toxicology, GSK*

- **Gwyn Morgan, DVM, PhD**

- Former Vice President of Safety Assessment, GSK*

- **Pharmacokinetics**

- **Edmund Capparelli, PharmD**

- Associate Clinical Professor of Pediatrics, Co-Director, Pediatric Pharmacology Research Unit, University of California, San Diego*

Emerging Resistance In Respiratory Pathogens

Problems and Solutions

Donald E. Low, MD
Microbiologist-in-Chief, Mount Sinai Hospital
Professor of Medicine, University of Toronto

Agenda

- Define the problem
 - emerging fluoroquinolone resistance in pneumococci
- Explain the clinical consequences
- Outline a strategy to deal with fluoroquinolone resistance
 - using the most potent fluoroquinolone

Gemifloxacin Key Attributes

- Functionally dual-targeting quinolone
- Potent *in vitro* activity and PK/PD parameters against *S. pneumoniae*
- Excellent activity against other respiratory pathogens
 - *H. influenzae* MIC₉₀ = 0.004-0.015 µg/mL
 - *M. catarrhalis* MIC₉₀ = 0.015 µg/mL
 - *M. pneumoniae* MIC₉₀ = 0.12 µg/mL
 - *C. pneumoniae* MIC₉₀ = 0.25 µg/mL
 - *L. pneumophilia* MIC₉₀ = 0.015 µg/mL

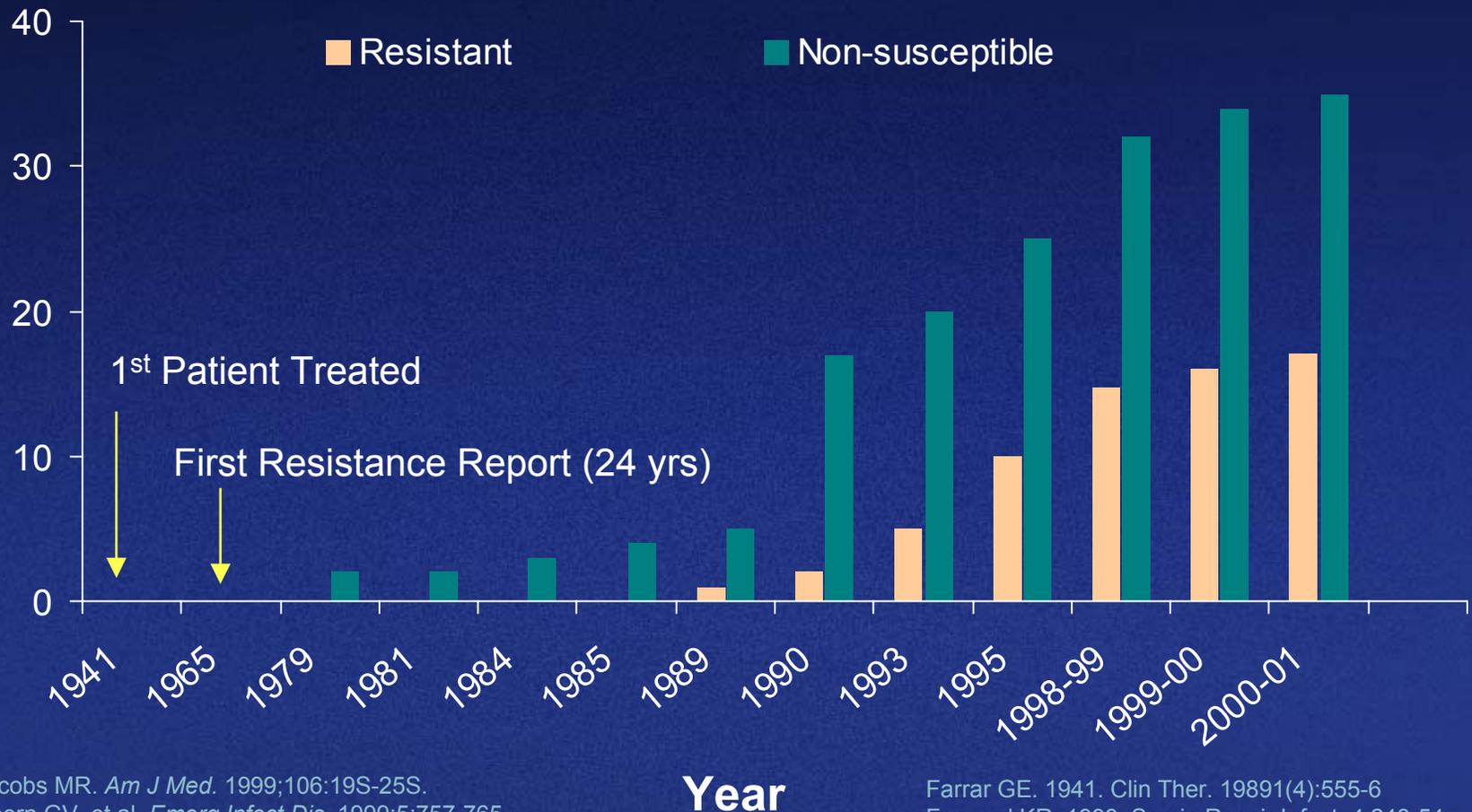
Defining the Problem

- *Streptococcus pneumoniae*
 - Most common bacterial cause of lower respiratory tract infections
 - Associated with the most significant morbidity and mortality
- Growing antimicrobial resistance to
 - β -Lactams
 - Macrolides
 - Tetracyclines
 - Trimethoprim/sulfa

Fluoroquinolones
*Academia and Industry Response to
Antimicrobial Resistance*

Penicillin Non-susceptible *S. pneumoniae* U.S. 1941-2001

Isolates (%)

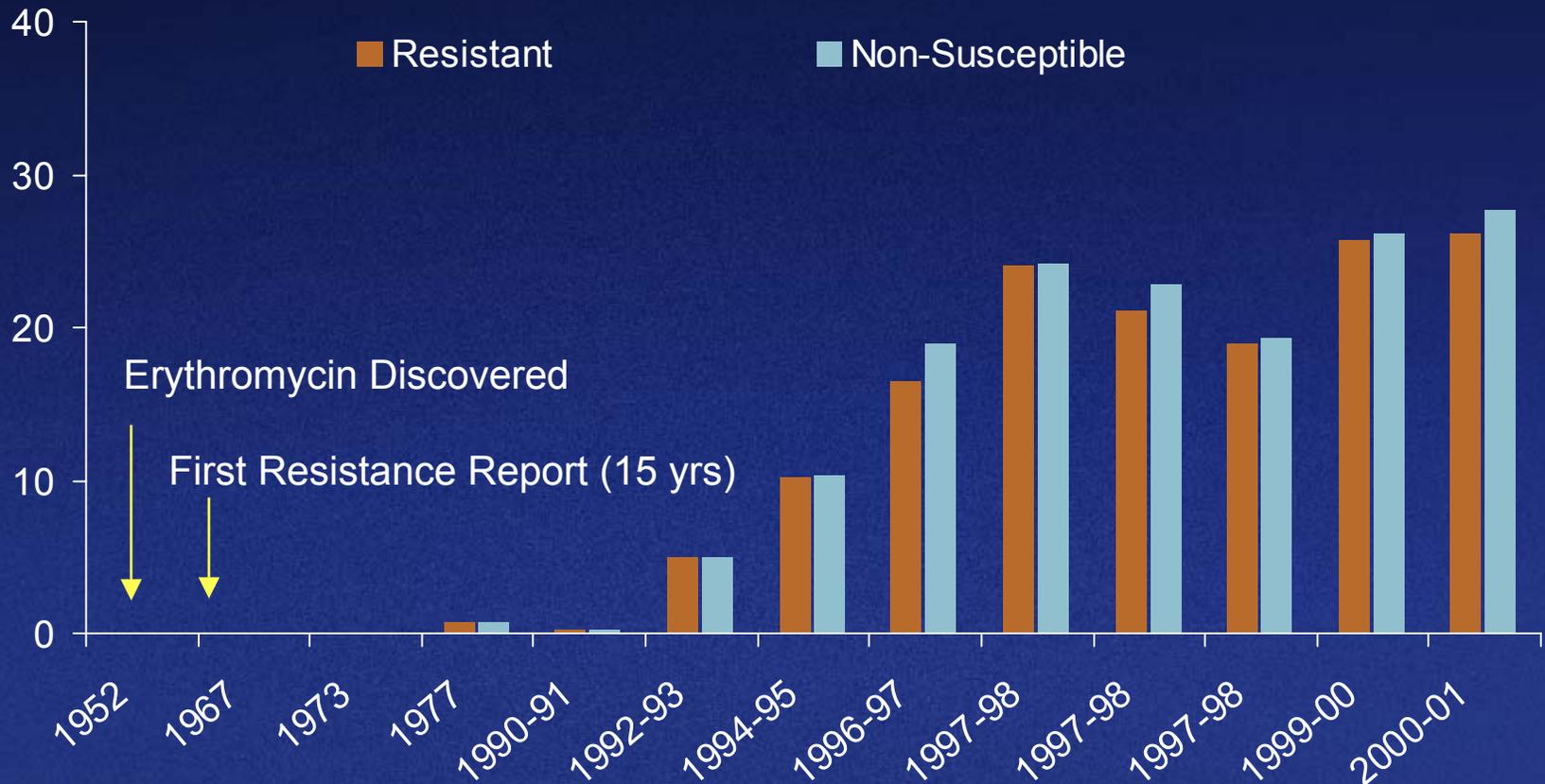


Jacobs MR. *Am J Med.* 1999;106:19S-25S.
Doern GV, et al. *Emerg Infect Dis.* 1999;5:757-765.
Thornsberrry C. et al. *Clin Infect Dis* 2002;34:S4-S16

Farrar GE. 1941. *Clin Ther.* 19891(4):555-6
Forward KR. 1999. *Semin Respir Infect.* 4:243-54.

Macrolide Non-susceptible *S. pneumoniae* U.S. 1952-2001

Isolates (%)



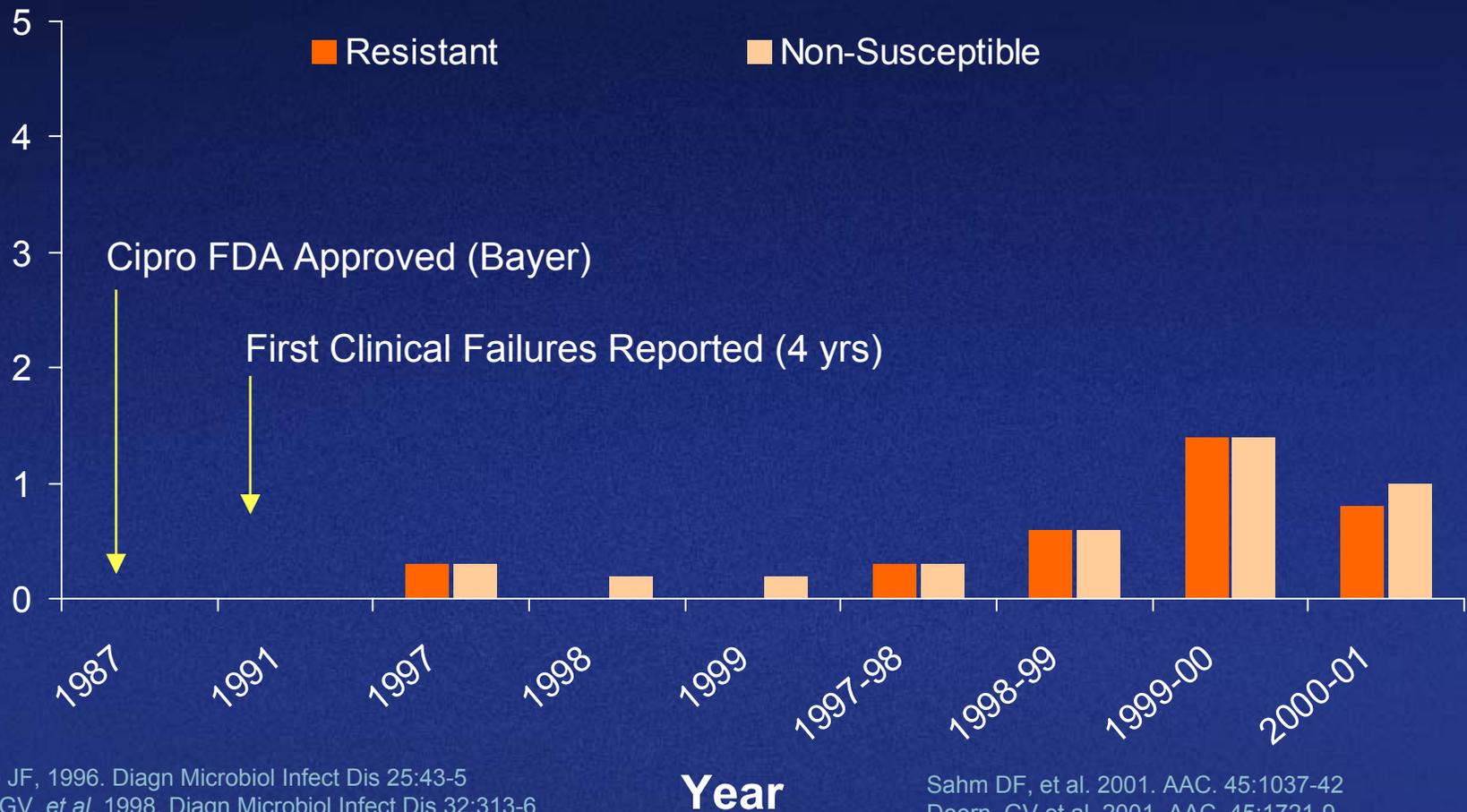
Kislak JW. 1967. N Engl J Med, 276:852.
 Weisblum B. 1967. Lancet, 1;843-4.
 Dixon JM et al. 1978. Can Med Assoc J. 119:1044-6.
 Jorgensen JH, et al. 1990 AAC 34:2075-80.
 Barry AL, et al. 1994. AAC. 38:2419-25

Year

Doern, GV. 1996. AAC 40:1208-13.
 Mason EO et al. 2000. JAC. 45:623-31.
 Sahm DF et al. 2000. AAC. 44:2521-4.
 Doern GV et al. 2001. AAC. 45:1721-9.
 Low DE et al. 2002. ASM General Meeting [Abstract]

Quinolone Non-susceptible *S. pneumoniae* U.S. 1987-2001

Isolates (%)

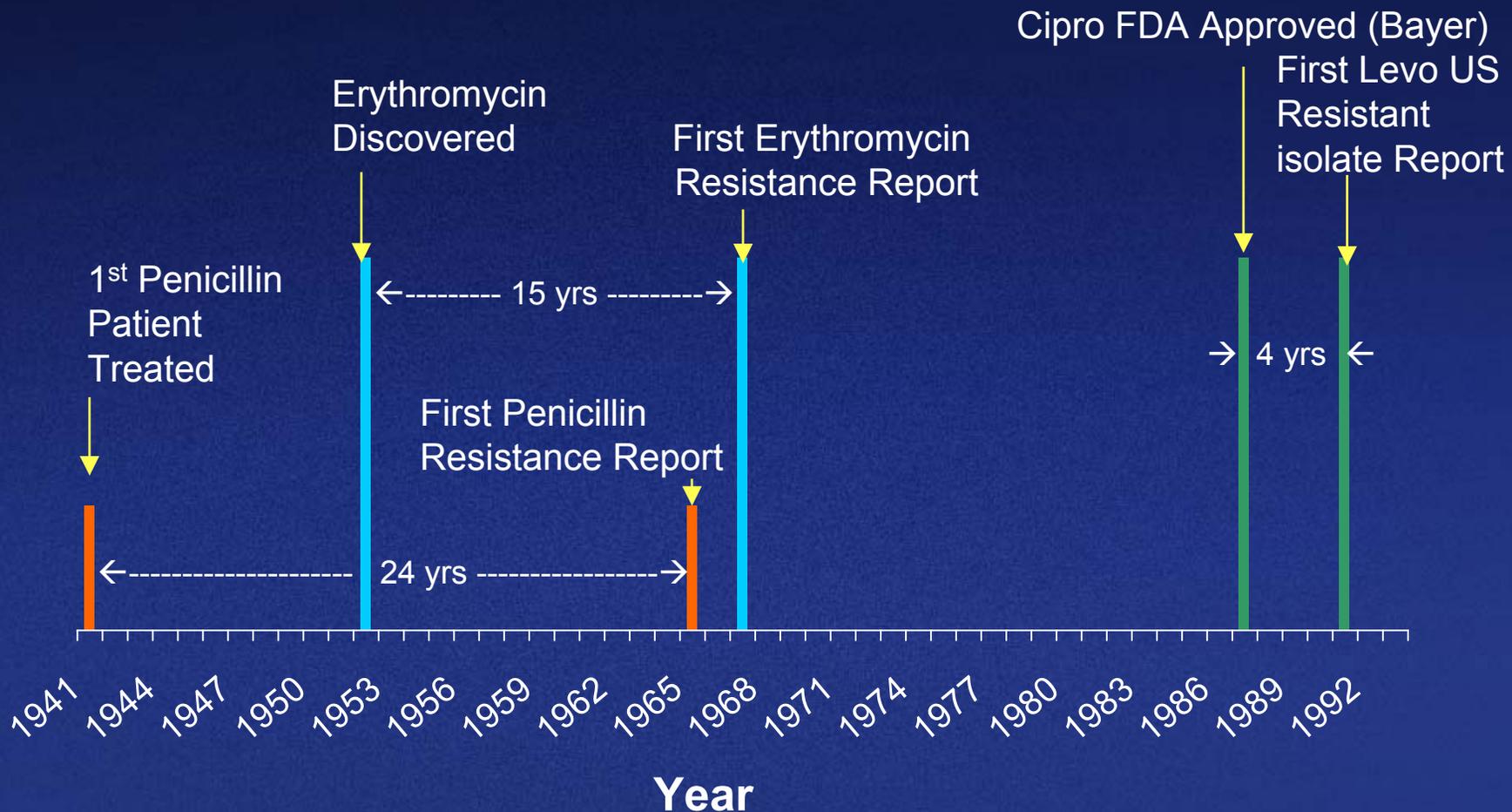


Plouffe JF, 1996. *Diagn Microbiol Infect Dis* 25:43-5
 Doern GV, et al. 1998. *Diagn Microbiol Infect Dis* 32:313-6
 MMWR, Sept 2001. 50(37):800-806
 Sahm DF, et al. 2000. *AAC*. 44:2521-4

Year

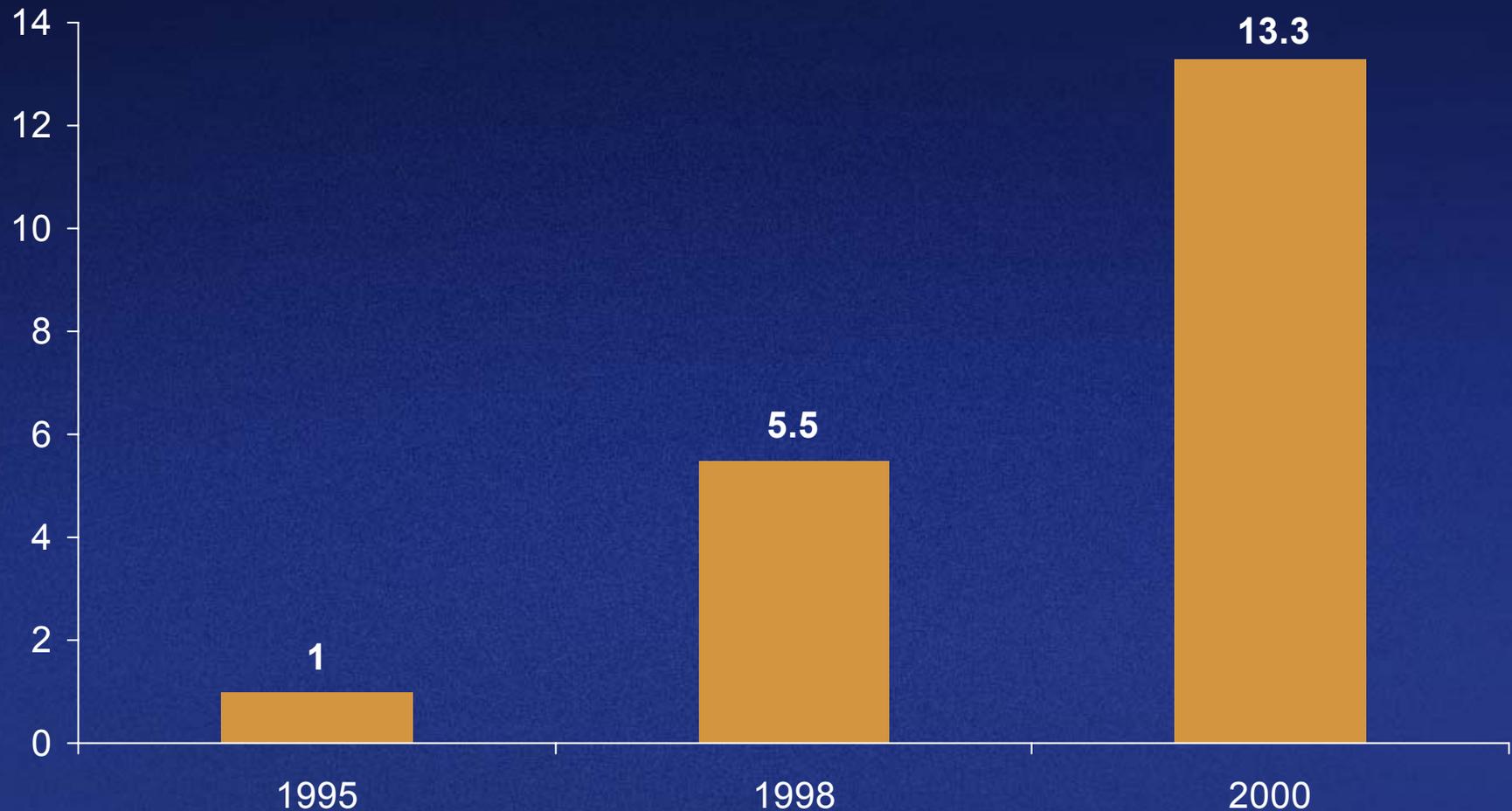
Sahm DF, et al. 2001. *AAC*. 45:1037-42
 Doern, GV et al 2001. *AAC*. 45:1721-9
 Low, DE, et al. 2002. *ASM 2002 [Abstract]*
 Lee et al. 1999, *NEJM*.325:520-521

S. pneumoniae Resistance Time Line U.S. 1941-1992



Levofloxacin-resistant *S. pneumoniae* Hong Kong 1995-2000

Isolates (%)



Ho PL, et al. J Antimicrob Chemother. 2001;48:659-665.

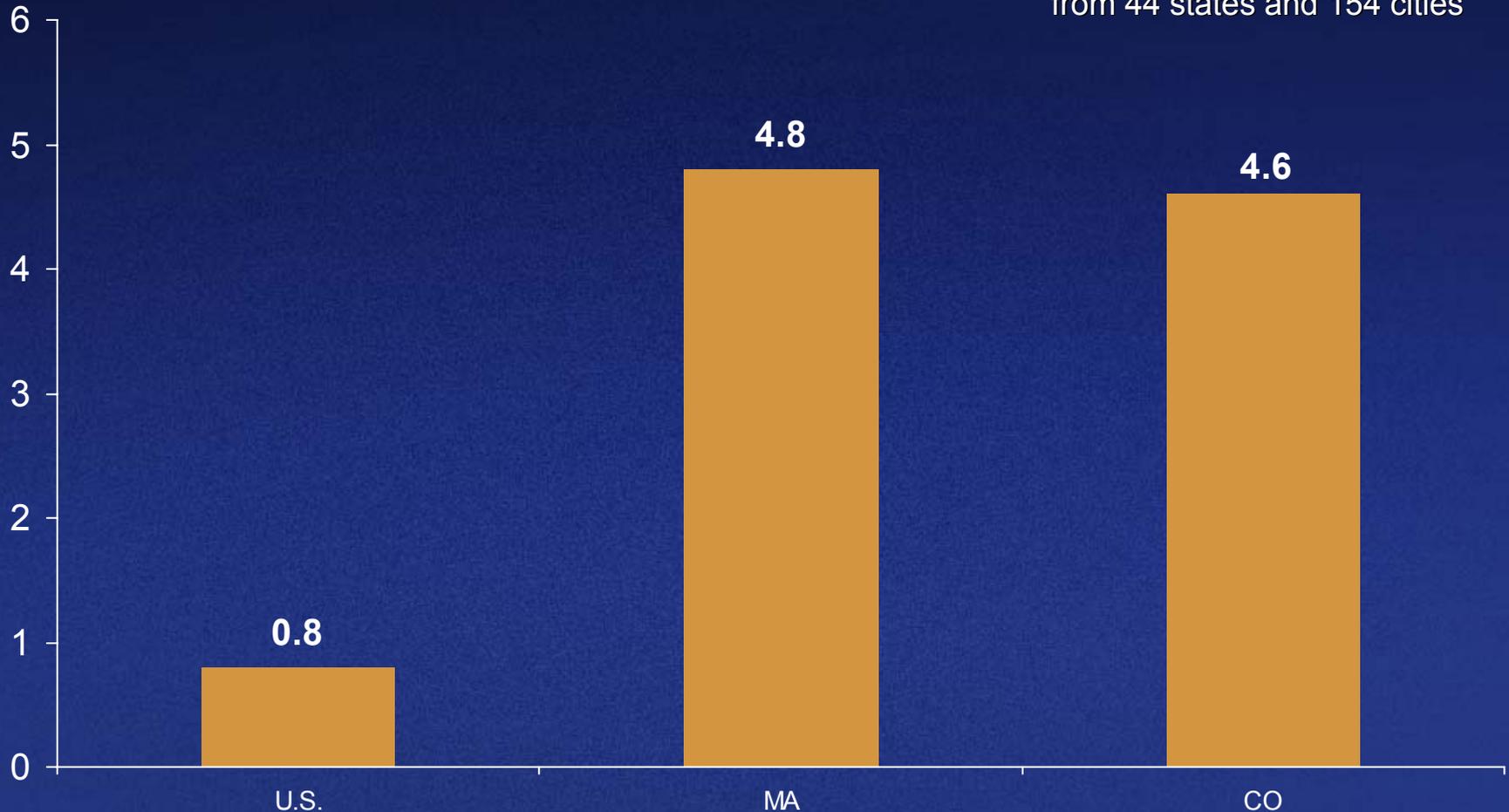
Ho PL, et al. Antimicrob Agents Chemother. 1999;43:1310-1313.

Increasing Levofloxacin-resistant *S. pneumoniae*

US Cities and States, Winter of 2000-2001

Isolates (%)

N=10,103 isolates
from 44 states and 154 cities



Clinical Implications

Resistance Leads to Treatment Failure & Even Death

Disease	# Patients Levofloxacin Resistant	Patient Outcome
Acute Bronchitis ¹	1	Treatment Failure
Pneumococcal Meningitis ²	1	Treatment Failure/Death
Hospital Acquired Pneumococcal Pneumonia ³	1	Treatment Failure
Community Acquired Pneumonia ⁴	4	4 Treatment Failures 1 Death
CAP, Sepsis, Meningitis ⁵	1	Treatment Failure/Death

1) Kuehnert et al. Ann Intern Med 1999. 2) Wortmann & Bennett CID 1999. 3) Empey et al. Ann of Pharmacother 2001.
4) Davidson, et al NEJM 2002. 5) Ross et al. NEJM 2002

Mechanism of Action of Fluoroquinolones

- Topoisomerase IV (ParC, ParE)
- DNA gyrase (GyrA, GyrB)

Development of Resistance to Fluoroquinolones

- Topoisomerase IV (~~ParC, ParE~~)
- DNA gyrase (GyrA, GyrB)

Development of Resistance to Fluoroquinolones

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Development of Resistance to Fluoroquinolones

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- DNA gyrase (GyrA, GyrB)

Gemifloxacin is Functionally Dual Targeting

Mutation	Levofloxacin		Gemifloxacin	
	MIC	Increase MIC	MIC	Increase MIC
None	0.038 (S)	NA	0.016 (S)	NA

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None	0.038 (S)	NA	0.016 (S)	NA
<i>parC</i>	1.5 (S)	32X		

Gemifloxacin is Functionally Dual Targeting

Mutation	Levofloxacin		Gemifloxacin	
	MIC	Increase MIC	MIC	Increase MIC
None	0.038 (S)	NA	0.016 (S)	NA
<i>parC</i>	1.5 (S)	32X	0.064 (S)	4X

Gemifloxacin is Functionally Dual Targeting

Mutation	Levofloxacin		Gemifloxacin	
	MIC	Increase MIC	MIC	Increase MIC
None	0.038 (S)	NA	0.016 (S)	NA
<i>parC</i>	1.5 (S)	32X	0.064 (S)	4X
<i>gyrA</i>	0.75 (S)	20X		

Gemifloxacin is Functionally Dual Targeting

Mutation	Levofloxacin		Gemifloxacin	
	MIC	Increase MIC	MIC	Increase MIC
None	0.038 (S)	NA	0.016 (S)	NA
<i>parC</i>	1.5 (S)	32X	0.064 (S)	4X
<i>gyrA</i>	0.75 (S)	20X	0.023 (S)	1.4X

Gemifloxacin is Functionally Dual Targeting

Mutation	Levofloxacin		Gemifloxacin	
	MIC	Increase MIC	MIC	Increase MIC
None	0.038 (S)	NA	0.016 (S)	NA
<i>parC</i>	1.5 (S)	32X	0.064 (S)	4X
<i>gyrA</i>	0.75 (S)	20X	0.023 (S)	1.4X
<i>parC</i> <i>gyrA</i>	>32.0 (R)	>1000X		

Gemifloxacin is Functionally Dual Targeting

Mutation	Levofloxacin		Gemifloxacin	
	MIC	Increase MIC	MIC	Increase MIC
None	0.038 (S)	NA	0.016 (S)	NA
<i>parC</i>	1.5 (S)	32X	0.064 (S)	4X
<i>gyrA</i>	0.75 (S)	20X	0.023 (S)	1.4X
<i>parC</i> <i>gyrA</i>	>32.0 (R)	>1000X	0.25 (S)	64X

Reservoir of 1st & 2nd Step Mutants in Untreated Patients with Pneumococcal Pneumonia

- Frequency of 1st-step mutations
 - $1/10^7$
- Frequency of 2nd-step mutations
 - $1/10^5$
- Number of bacteria in lung in pneumococcal pneumonia
 - 10^{12} to 10^{14}
- Number of mutated bacteria in pneumococcal pneumonia
 - 10^5 – 10^7 isolates with 1st-step mutation
 - Up to a hundred isolates with 1st and 2nd step mutation

†Frisch, A.W. J Exp Med 1942, Pestova et al. J Antimicrob Chemother 2000, Li et al. Antimicrob Agents Chemother 2002, Gillespie et al. 3rd International Symposium on Pneumococci and Pneumococcal Disease 2002

TB Resistance

A Precedent for Quinolone Resistance

Mutations Rendered Single-Agent
Anti-TB Therapy Useless

Mutations Rendered Single-Agent Anti-TB Therapy Useless

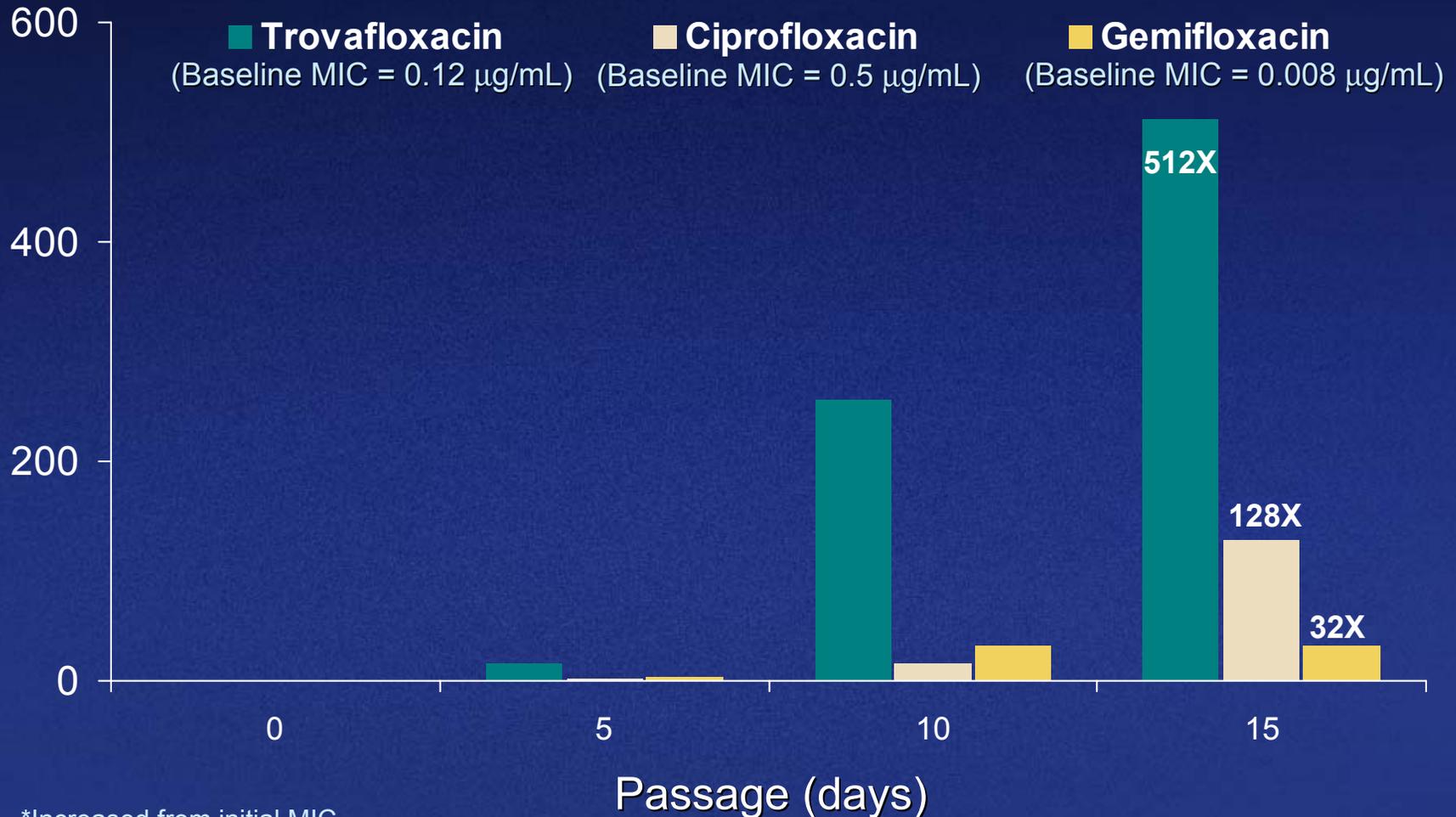
Drug	Target	Mutation Frequency	MIC ($\mu\text{g/mL}$)	
			Wild Type	Mutant
Isoniazid	Catalase-Peroxidase	10^{-7}	0.09	200
Ethambutol	Arabinosyl transferase	10^{-7}	0.25	>50
Streptomycin	Ribosomal protein S12 / 16S _{RNA}	10^{-7}	0.25	>500

Khoo et al J Biol Chem 1996;271:28682-90, David et al Appl Microbio 1970;20:810-4

In Vitro Development of Resistance

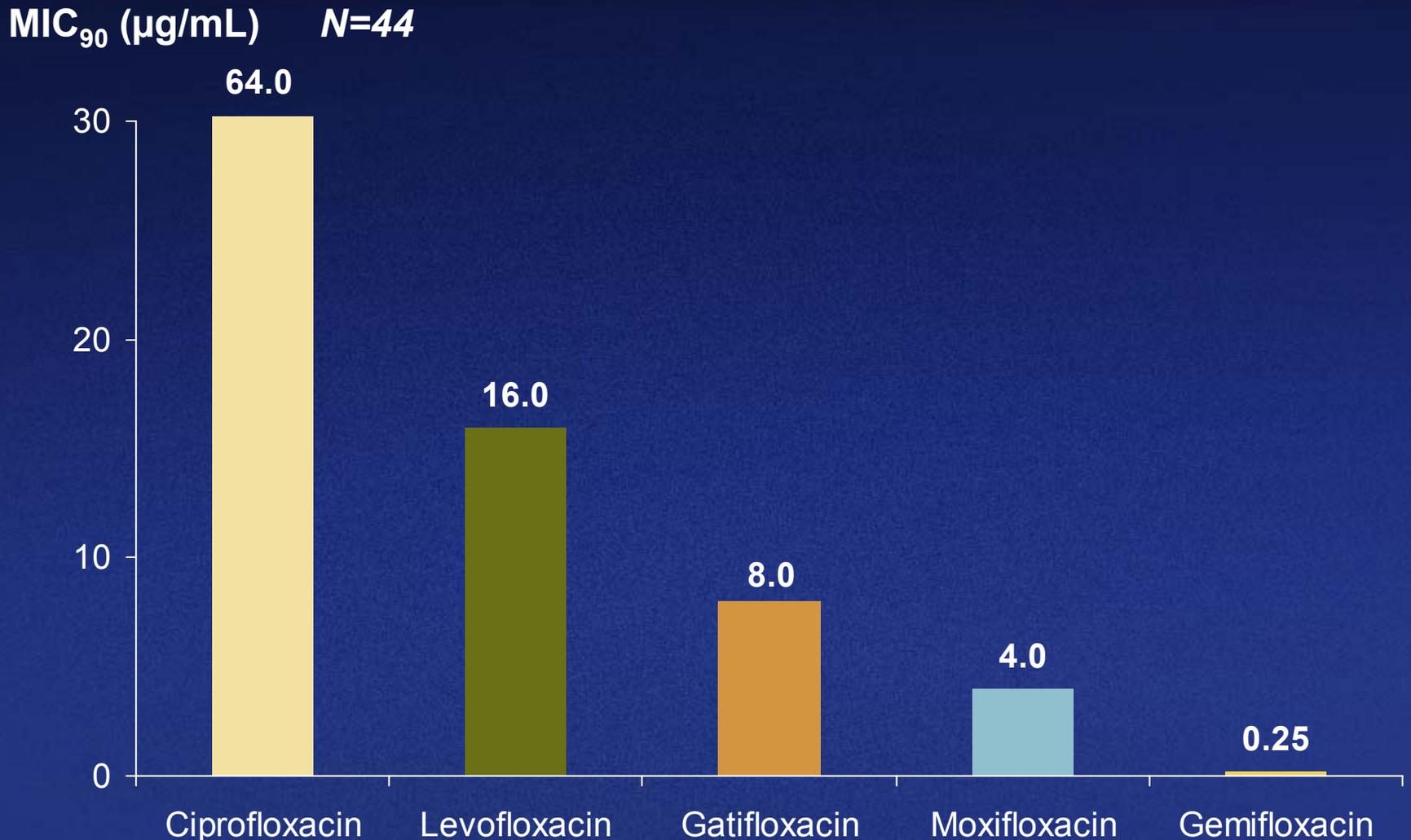
S. pneumoniae ATCC 49619

Fold increase in MIC*

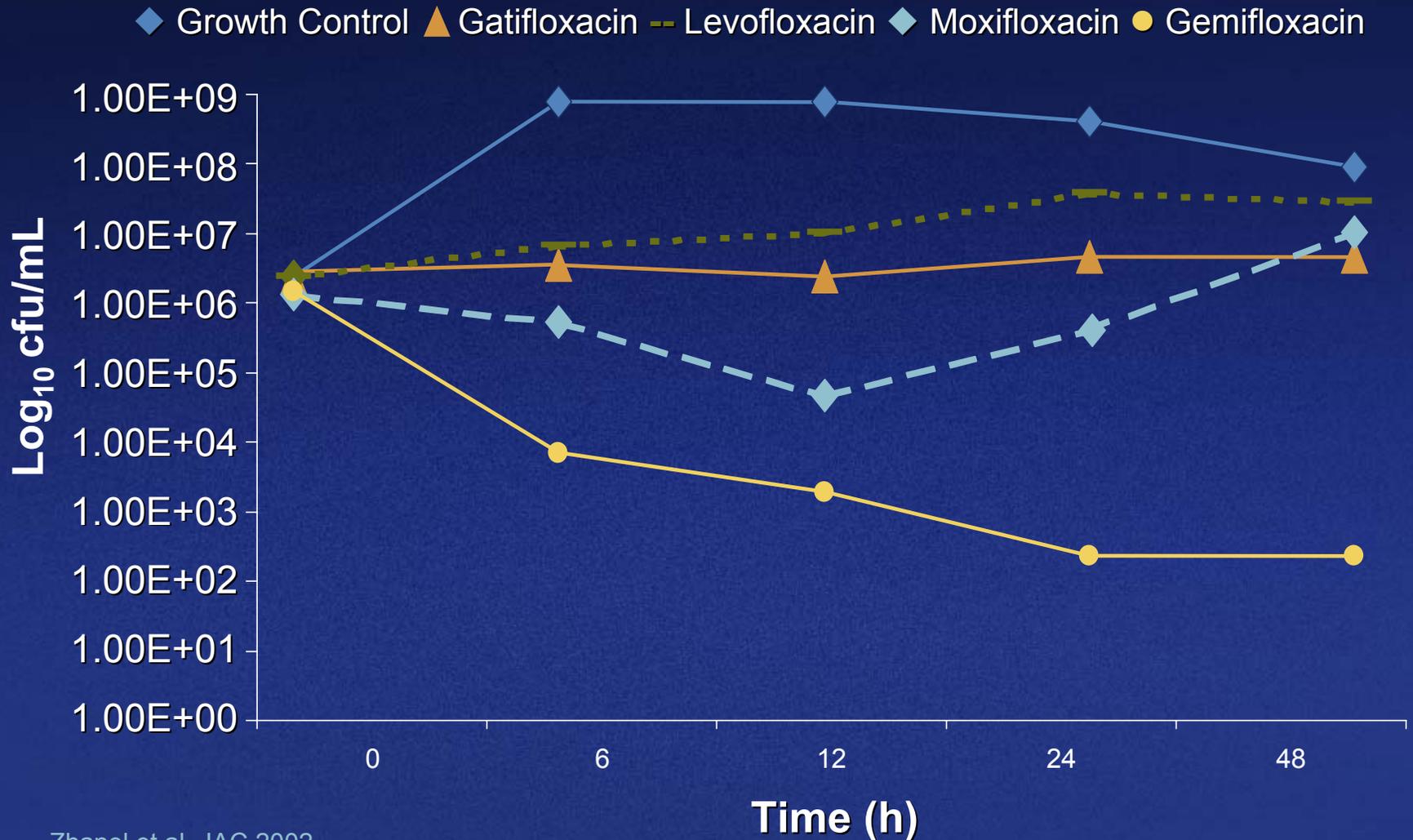


*Increased from initial MIC

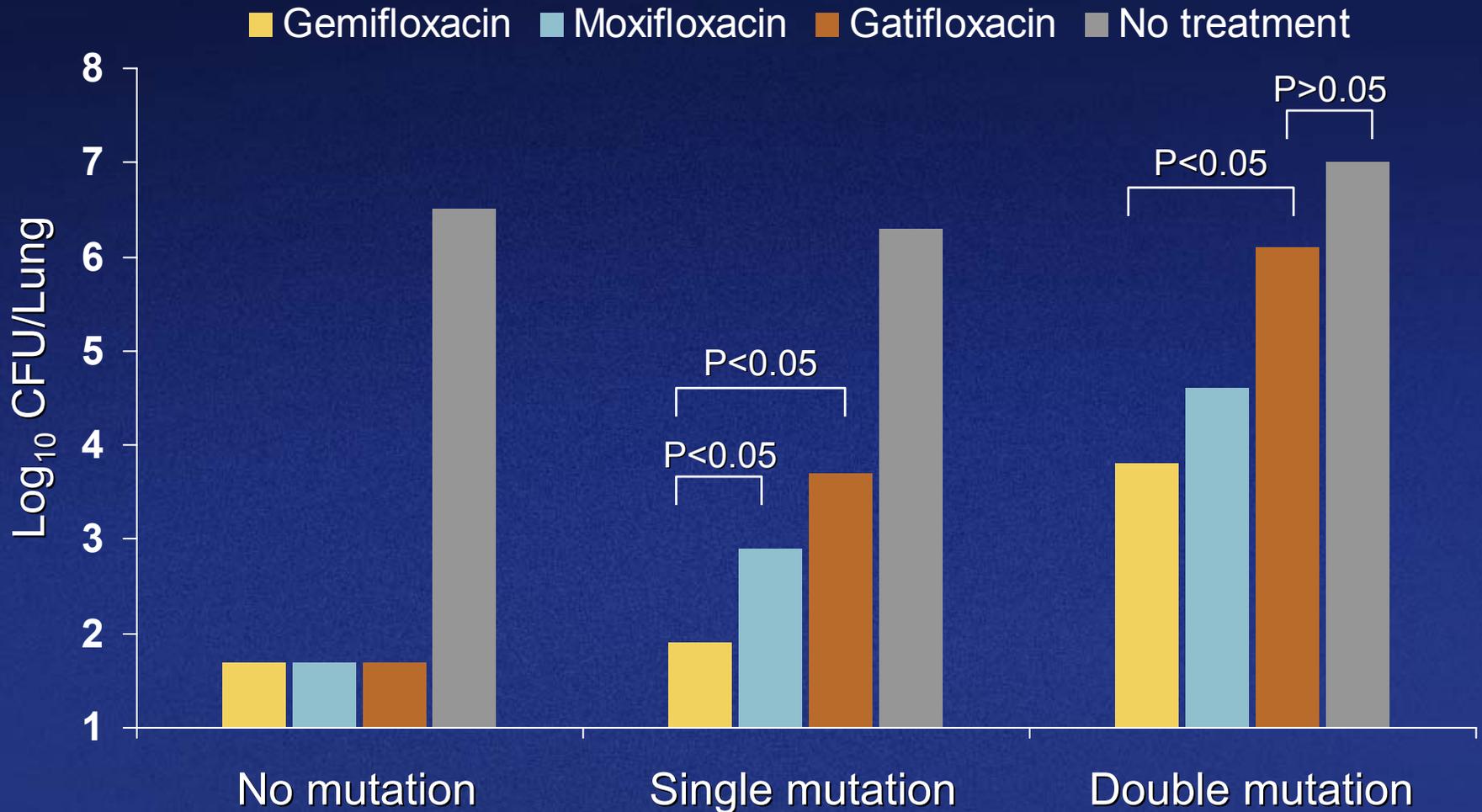
Gemifloxacin: Most Active Fluoroquinolone Against 2nd Step *S. pneumoniae* Mutants



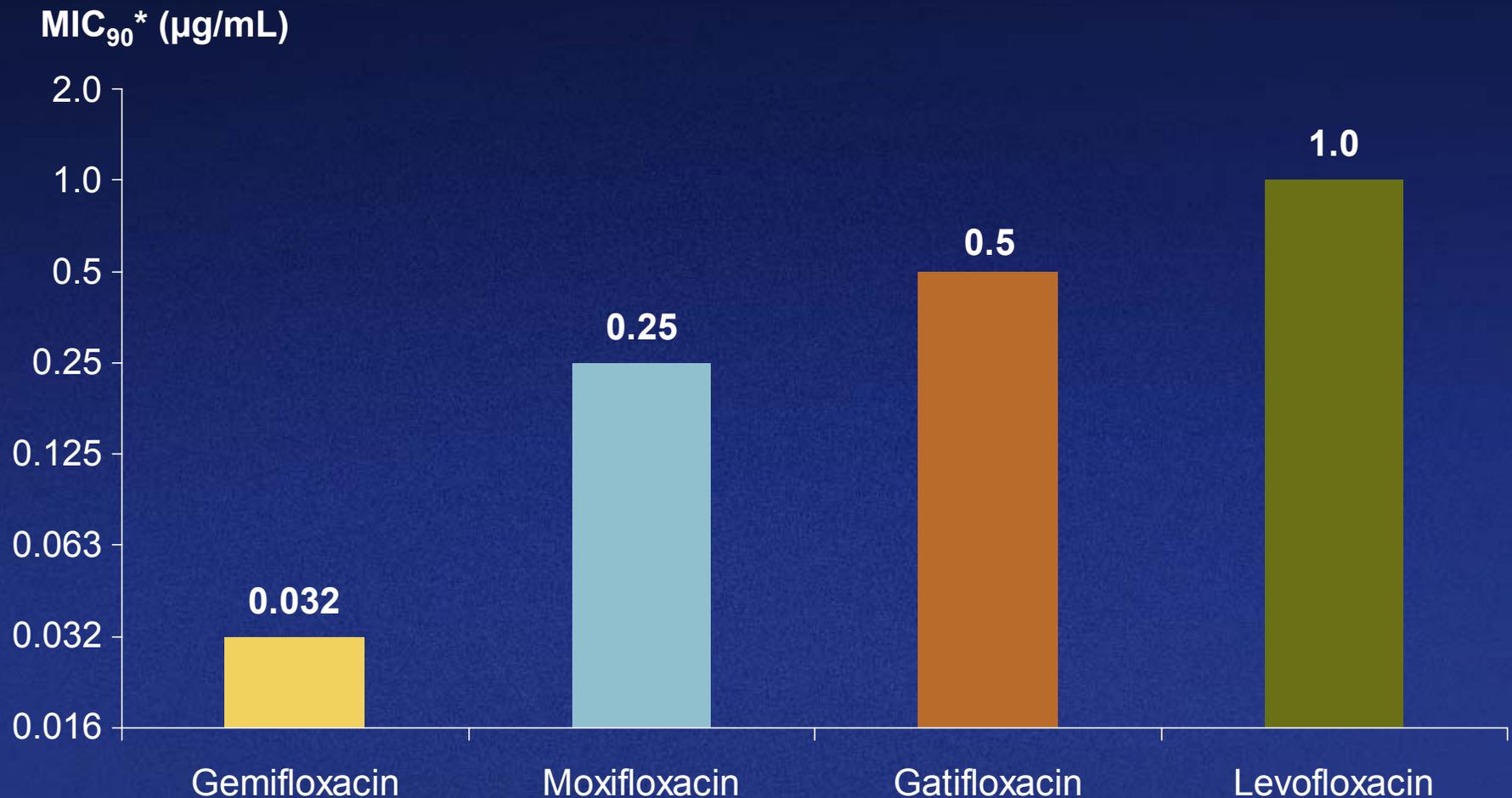
Fluoroquinolone Killing of a Quinolone-Resistant *S. pneumoniae* Isolate Simulating Free AUC/MIC Ratios



In Vivo Efficacy of Gemifloxacin, Moxifloxacin and Gatifloxacin Against *S. pneumoniae*

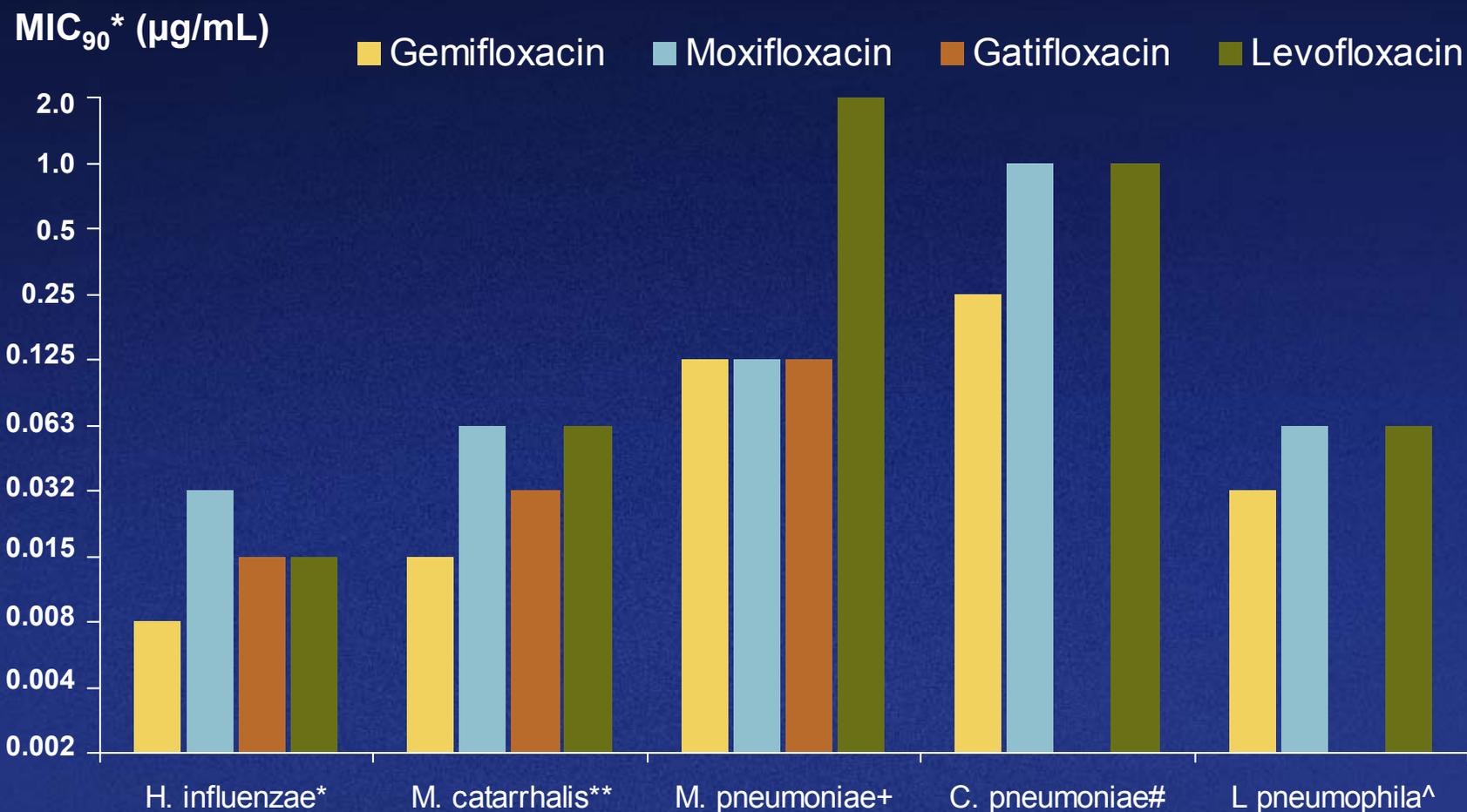


Gemifloxacin Demonstrates the Lowest MIC₉₀ Against *S. pneumoniae*



*Data on file, GSK [2000 Alexander Project-N.A. (n=1065)] and [2001 Jacobs Study-US (n=550)].
ICAAC 2000 [Hoban et al.-N.A. (n=1450)]

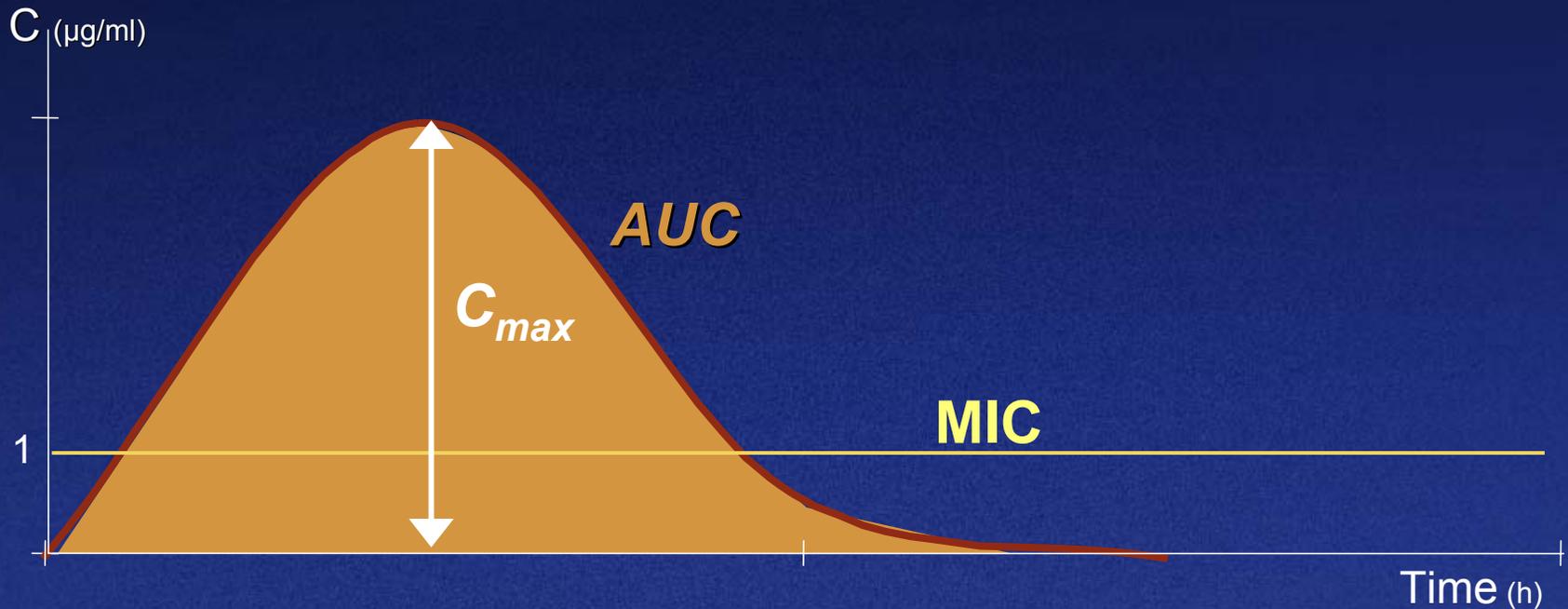
Gemifloxacin Demonstrates Comparable MIC₉₀ Against Other Respiratory Pathogens



*Data on file, GSK [2000 Alexander Project-Global (n=2764)] and [2001 Jacobs Study-US (n=290)]; **Data on file, GSK [2000 Alexander Project-Global (n=250)] and [2001 Jacobs Study-US (n=205)]; +Waites et al., ASM 2001 (n=103); #Roblin et al., AAC. 1999 (n=20); ^Yu et al., ICAAC 2000 [(n=68) all strains were *L. pneumophila* serogroup I].

Predictors of Bacterial Eradication & Clinical Efficacy

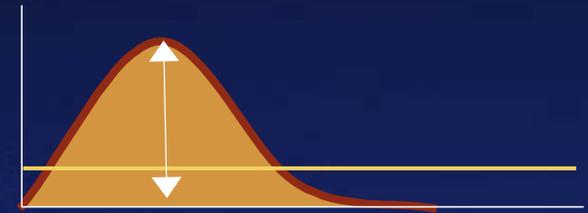
PK/PD Profile for Quinolones



- AUC/MIC - target $> 25-30$
- C_{max}/MIC - target > 10

Predictors of Bacterial Eradication & Clinical Efficacy for *M. catarrhalis*

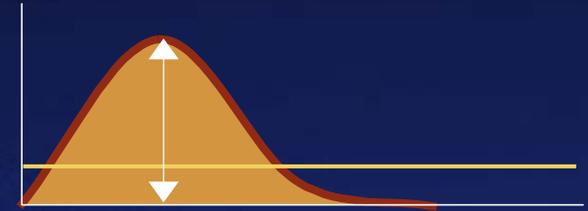
PK/PD Profile for Ciprofloxacin



		Target	Actual
AUC/MIC	17/0.06	>100	283
C _{max} /MIC	2.1/0.06	>10	35

Predictors of Bacterial Eradication & Clinical Efficacy for *S. pneumoniae*

PK/PD Profile for Gemifloxacin



Target

Actual

AUC/MIC

2.9-3.8/0.03

>25

97-127

C_{max}/MIC

0.56-0.72/0.03

>10

19-24

Gemifloxacin has the Most Favorable Quinolone PK/PD Profile

Free Drug	AUC₂₄/MIC₉₀	C_{max}/MIC₉₀
Gemifloxacin (320 mg)	97-127	19-24
Moxifloxacin (400 mg)	96	9.2
Gatifloxacin (400 mg)	82	6.8
Levofloxacin (500 mg)	30-36	3.5-4.3

Gemifloxacin Susceptibility in Eight Levofloxacin Treatment Failures

- All isolates obtained at baseline susceptible to gemifloxacin
- 5/8 patient's isolates susceptible to gemifloxacin following emergence of levofloxacin resistance, isolates R and I to moxifloxacin & gatifloxacin
- Isolate from patient who died was gemifloxacin sensitive

Gemifloxacin Summary

- Excellent *in vitro* activity
- Excellent *in vivo* efficacy
- Most active against quinolone resistant strains
- Help preserve fluoroquinolone class
- Most effectively treat patients

Gemifloxacin – Efficacy Review

Lionel A. Mandell, MD, FRCPC

Professor of Medicine,
Chief, Division of Infectious Diseases
McMaster University

***Infectious Diseases is the only
medical specialty where the
implications of treatment go far
beyond the individual patient***

Agenda

- Impact of AECB and CAP
- Challenges in the treatment of AECB and CAP
- Has gemifloxacin demonstrated
 - clinical effectiveness in AECB?
 - unique / differentiable features in AECB?
 - clinical effectiveness in CAP?
 - unique / differentiable features in CAP?

Impact of Acute Exacerbation of Chronic Bronchitis (AECB)

- At least 13 million cases annually in U.S.
- *H. influenzae* and *S. pneumoniae* are major bacterial pathogens; emerging resistance now a major issue
- Up to 30% mortality rate in hospitalized patients

Impact of Community–Acquired Pneumonia (CAP)

- 3-4 million annual reported cases in US
- 600,000 hospitalizations
- 64 million days of restricted activity
- 64,000 deaths annually
- Pneumonia is seventh leading cause of death overall
- #1 cause of death from infection

Challenges in Treatment of AECB and CAP

- Increasing fluoroquinolone resistance in AECB and CAP
 - Treatment Failures
 - Deaths
- Growth in vulnerable patient population
 - Co-morbidities/co-medications
 - Need to maintain mobility & reduce hospitalization

**Has Gemifloxacin Demonstrated
Clinical Effectiveness in AECSB?**

Gemifloxacin 320mg Demonstrated Clinical Effectiveness in AECB Non-Inferiority Trials

Principal Studies

(N=826)

(N=826)

Study 068	<i>Gemifloxacin: 5 days</i> vs. <i>Clarithromycin: 7 days</i>
Study 070	<i>Gemifloxacin: 5 days</i> vs. <i>Amoxicillin/ Clavulanate: 7 days</i>
Study 212	<i>Gemifloxacin: 5 days</i> vs. <i>Levofloxacin: 7 days</i>

Supportive Studies

(N=441)

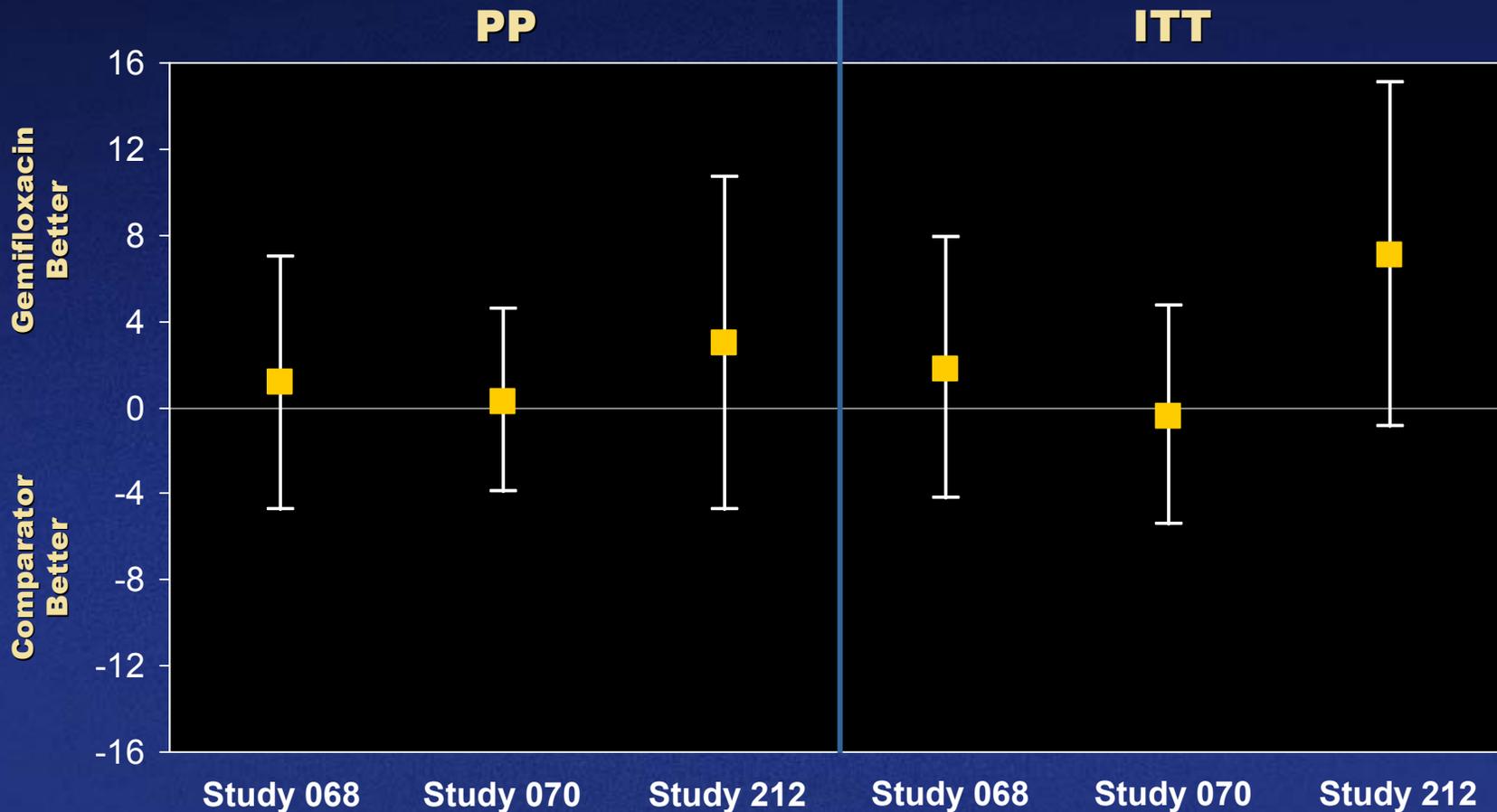
(N=450)

Study 069	<i>Gemifloxacin: 5 days</i> vs. <i>Trovafloxacin: 5 days</i>
Study 207	<i>Gemifloxacin: 5 days</i> vs. <i>IV Ceftriaxone: 1-3 days PO Cefuroxime: 7 days</i>

Long-term follow-up studies: 112, 139 (068 extension)

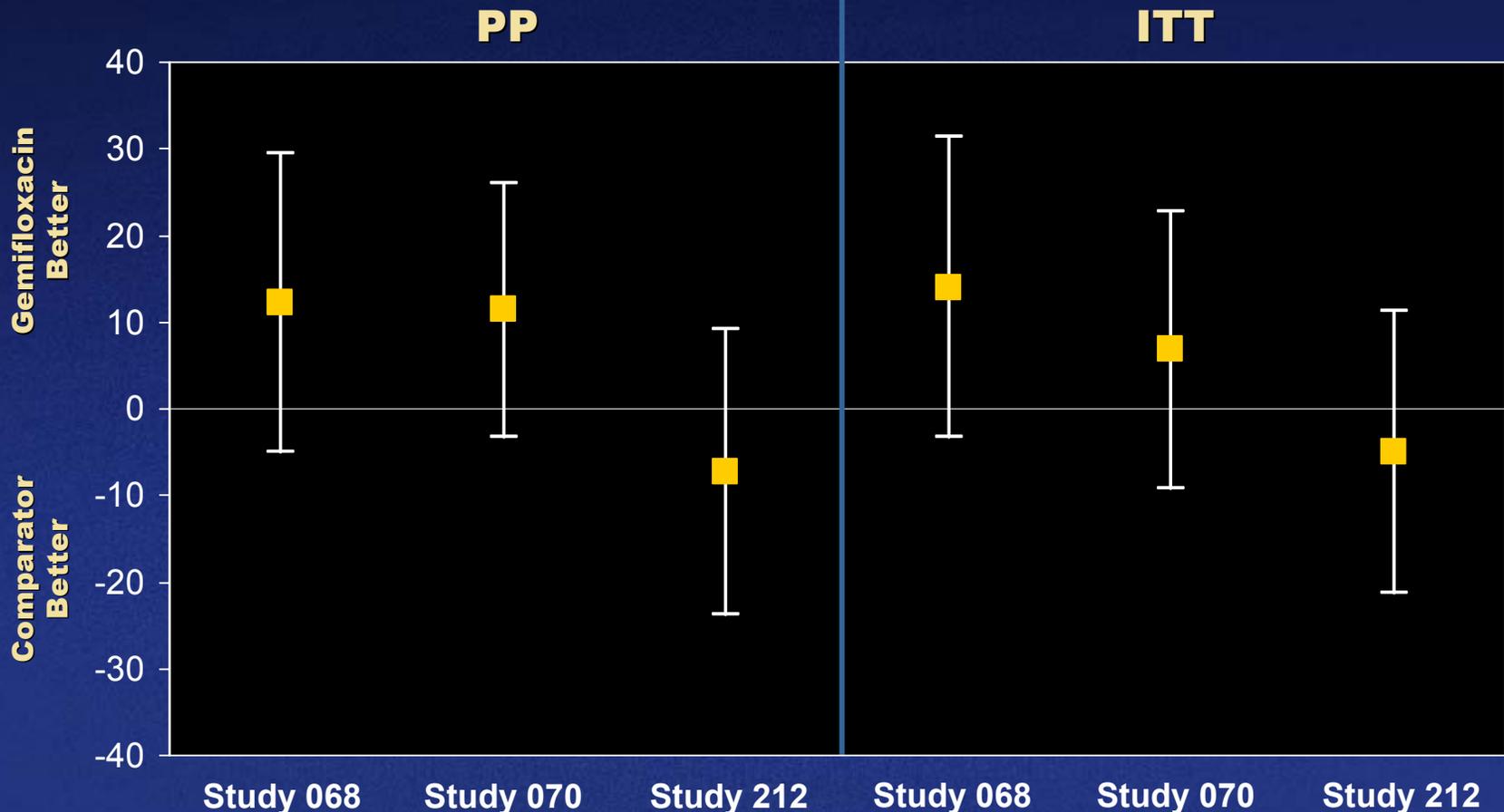
AECB Clinical Success

Treatment Difference
at Follow-Up(%; 95% CI)



AECB Bacteriological Success

Treatment Difference
at Follow-Up(%; 95% CI)



Gemifloxacin Has Demonstrated Clinical Effectiveness in AECB

- 3/3 principal studies meet non-inferiority criteria
- Equivalent to comparator in primary clinical endpoints in three principal studies (068, 070, 212)
- High bacteriologic success rates
- 5 days of gemifloxacin as effective as 7-10 days of comparators

**Does Gemifloxacin Have Unique /
Differentiable Features in AECB?**

Gemifloxacin

Unique / Differentiable Features in AECSB

- Faster bacteriological eradication than clarithromycin (study 068)
- Significantly more patients relapse-free compared to clarithromycin and trend towards fewer patients hospitalized (study 139)
- Statistically superior to IV/PO cephalosporin (study 207, ITT)
- Less time spent in hospital compared to IV/PO cephalosporin (study 207)
- Statistically superior clinical success compared to potent quinolone trovafloxacin (study 069, ITT)

Faster *H. influenzae* Eradication Compared to Clarithromycin

Bacterial Persistence (%)

**Gemifloxacin
x 5 days
N = 12**

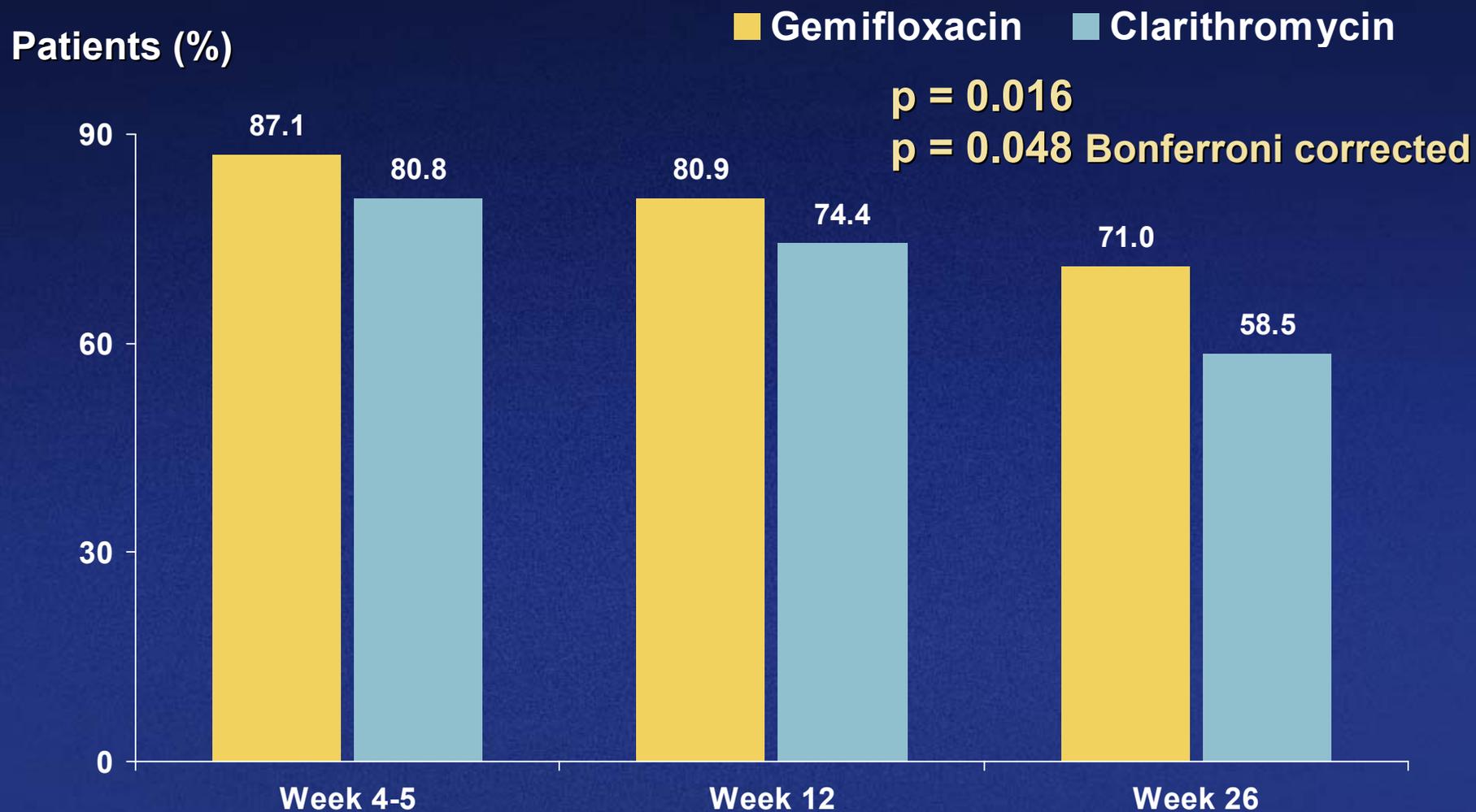
**Clarithromycin
x 7 days
N = 12**

Day 0	100	100
Day 1	0	50
Day 2	0	25
Day 3	0	25
Day 4	0	17
Day 5	0	8
Day 6	0	8

More Patients Relapse-Free with Gemifloxacin

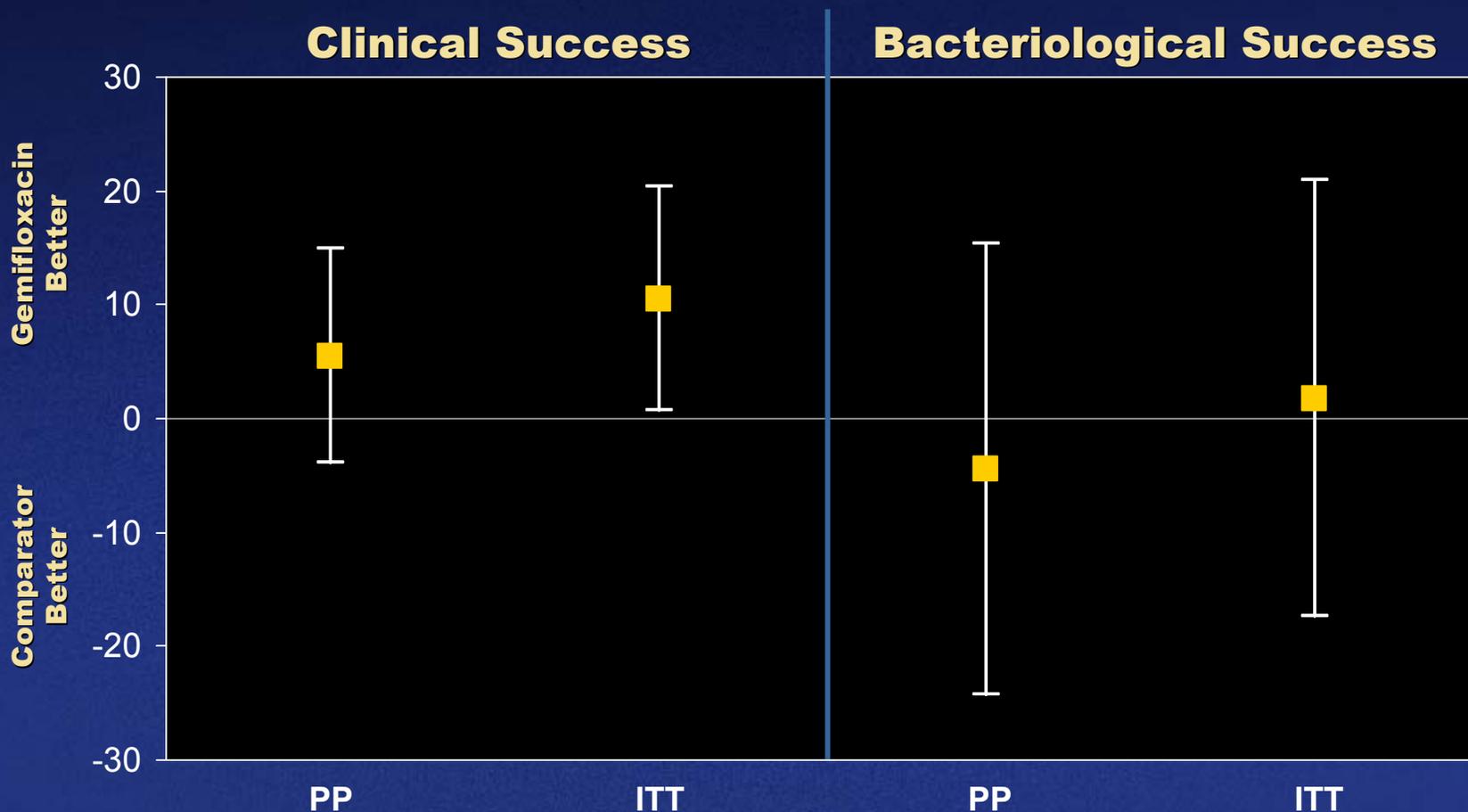
Study 068 Extension

AECB
STUDY
139



PO Gemifloxacin 5 Days Statistically Superior to 7-10 Days IV/PO Cephalosporins in Severe Disease (ITT)

Treatment Difference
at Follow-up (%; 95% CI)



Statistically Significant Reduction in Median Duration of Hospitalization

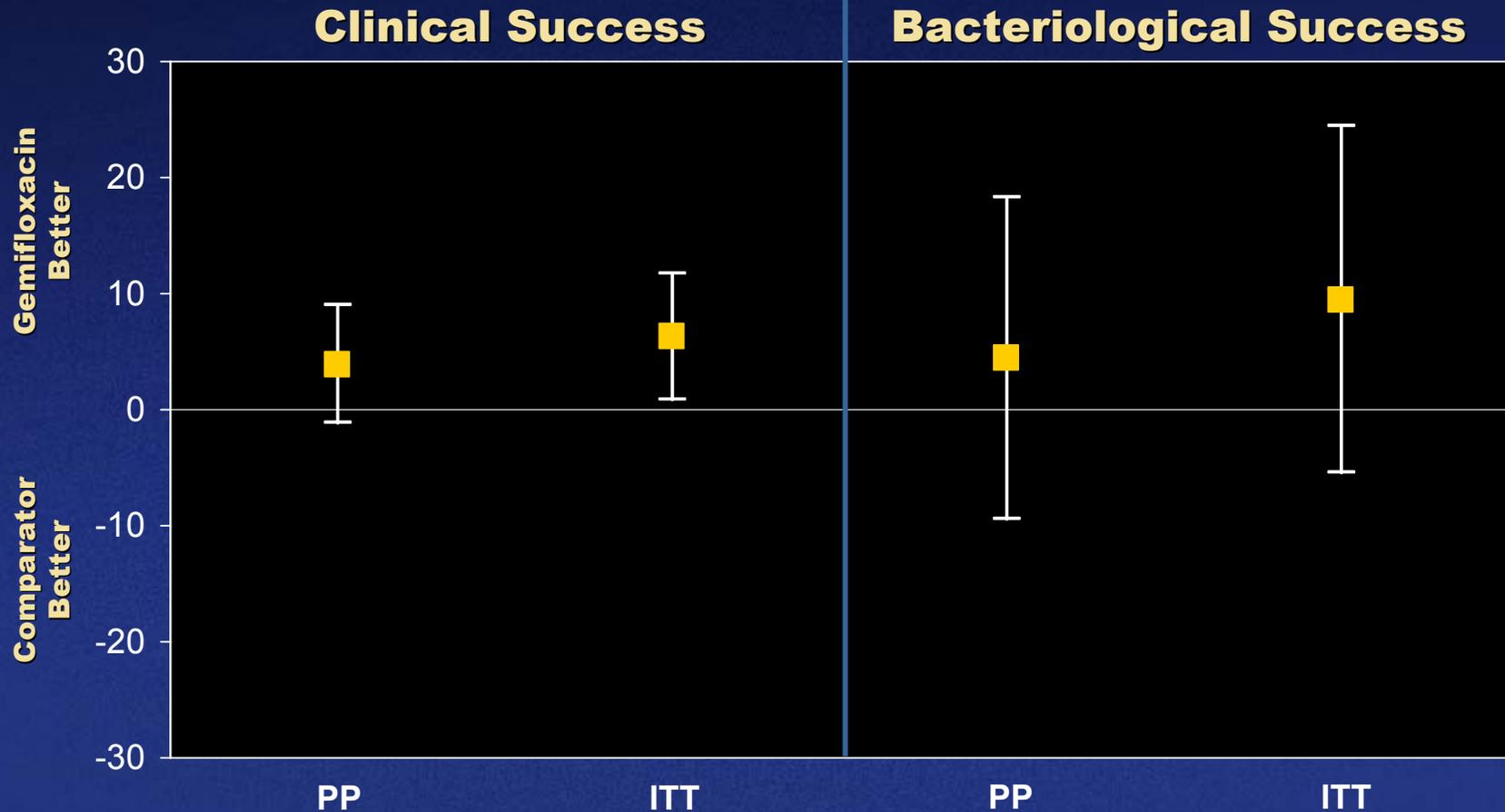
Gemifloxacin
N = 138

**Ceftriaxone IV /
Cefuroxime PO**
N = 136

	<i>n</i>	%	<i>n</i>	%
% Patients discharged (n)	120	87.0%	111	81.6%
Median time to discharge	9 days		11 days	
p value	0.04			

Statistically Superior Clinical Success Compared to Trovafloxacin (ITT)

Treatment Difference
at Follow-up (%; 95% CI)



**Has Gemifloxacin Demonstrated
Clinical Effectiveness in CAP?**

Gemifloxacin 320mg Demonstrated Clinical Effectiveness in CAP Non-inferiority Studies

Principal Studies

(N=947)

(N=927)

DOUBLE
BLIND

OPEN

Study 011	Gemifloxacin: 7 days	vs.	Amoxicillin/ Clavulanate: 10 days
Study 012	Gemifloxacin: 7 or 14 days	vs.	Clarithromycin/ Cefuroxime: 7 or 14 days
Study 049	Gemifloxacin: 7 or 14 days	vs.	Trovafloxacin: 7 or 14 days
Study 185	Gemifloxacin: 7-14 days	vs.	IV Ceftriaxone 1-7 days PO Cefuroxime: 1-13 days (± Macrolide)

Supportive Studies (N=402)

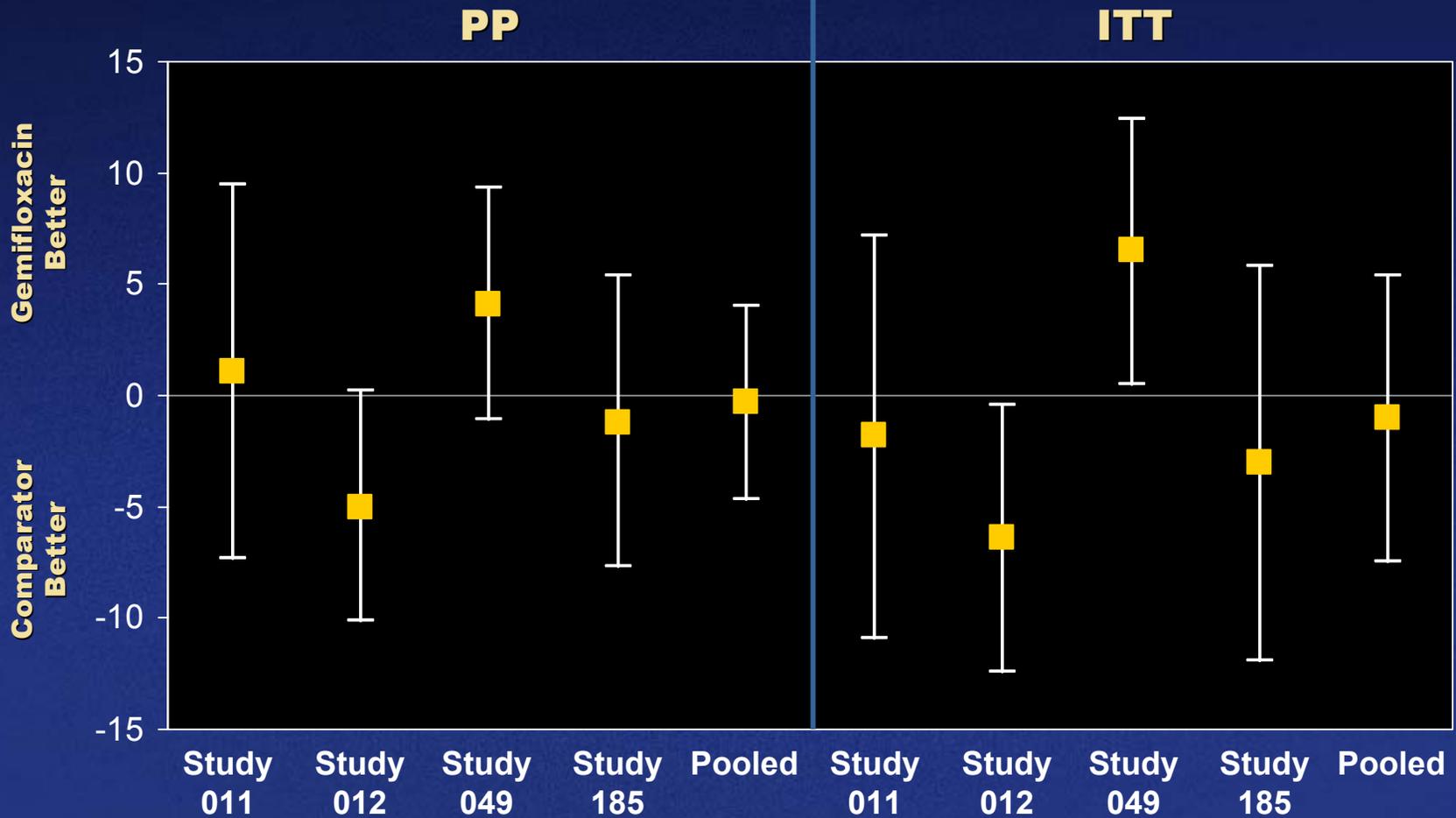
Study 061*	Gemifloxacin: 7 days (*CAP and AECB)
Study 287	Gemifloxacin: 7 days

Key CAP Demographics

Demographic/Baseline Characteristic	Gemifloxacin N=1349		Pooled Comparators N=927	
	<i>n</i>	%	<i>n</i>	%
Severe/Risk Class IV-V	129	9.6%	95	10.2%
Hospitalized Patients	760	56.3%	539	58.1%
Bacteremic Patients	62	4.6%	53	5.7%
Severe CAP, Hospitalized or Bacteremic	784	58.1%	563	60.7%
Patients \geq 65 yr	441	32.7%	312	33.7%

CAP Clinical Success

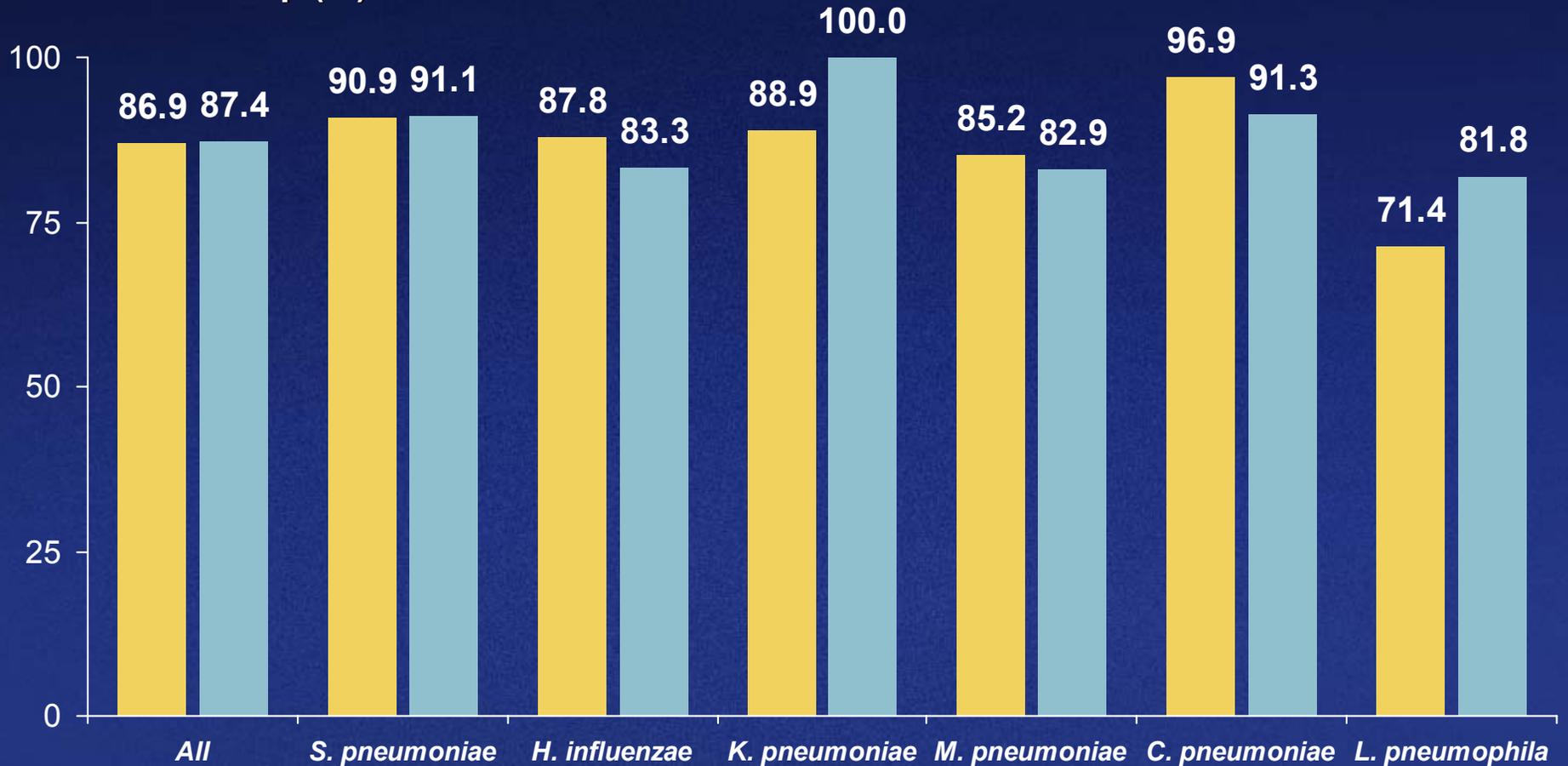
Treatment Difference
at Follow-Up (%; 95% CI)



Effective Pathogen Eradication 7 Days Gemifloxacin

Eradiation Rate*
At Follow Up (%)

■ Gemifloxacin ■ Pooled Comparator



*eradicatated or presumed eradicatated

Gemifloxacin Has Demonstrated Clinical Effectiveness in CAP

- 3/4 principal studies meet non-inferiority criteria

**Does Gemifloxacin Have Unique /
Differentiable Features in CAP?**

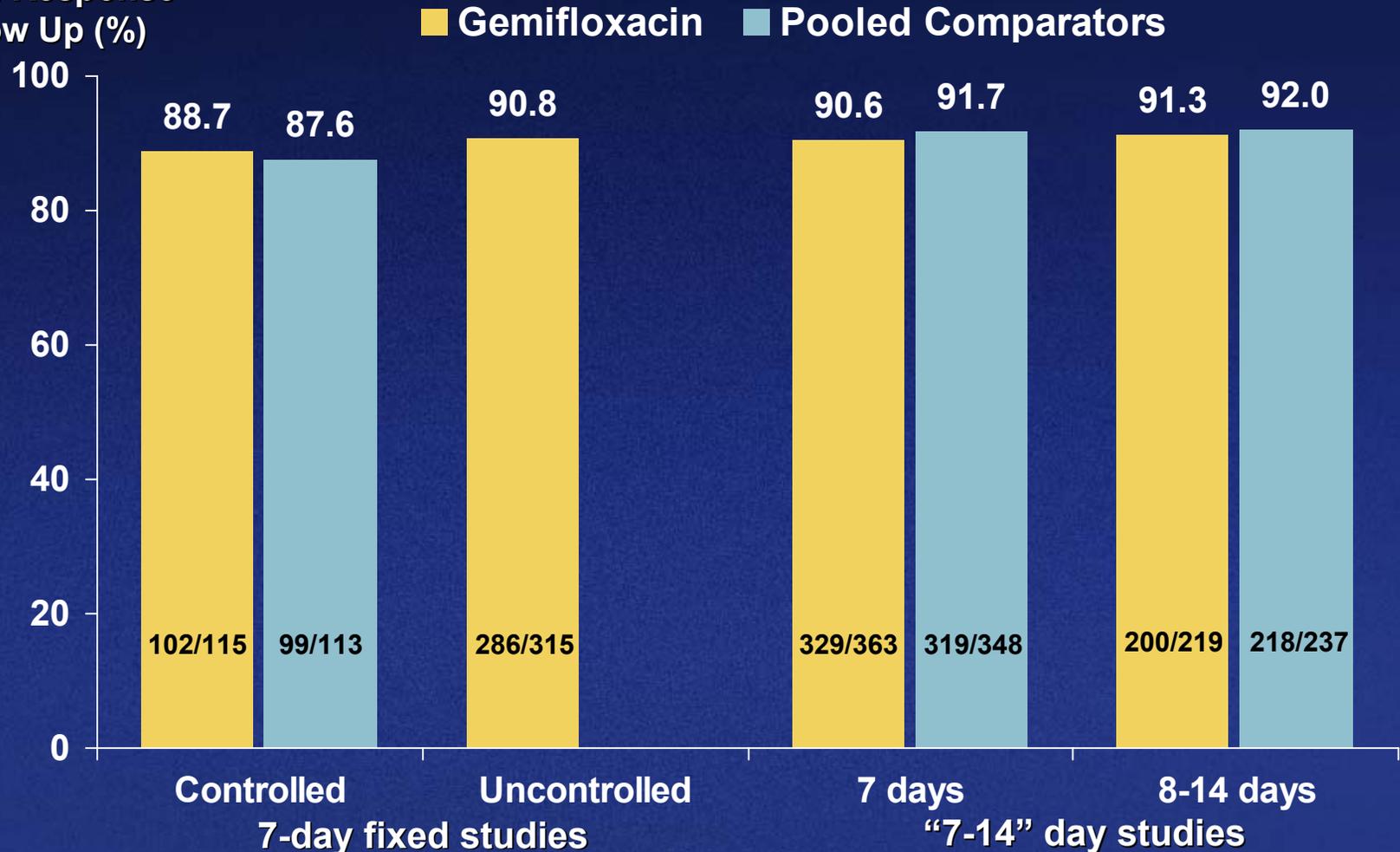
Gemifloxacin

Unique / Differentiable Features in CAP

- 7 days treatment effective for all severities of CAP
- Oral gemifloxacin as effective as IV ceftriaxone/oral cefuroxime in hospitalized patients (study 185)
- Gemifloxacin superior in head to head against potent quinolone trovafloxacin (study 049, ITT)
- Effective in eradicating PRSP, MRSP, CRSP, and ciprofloxacin non-susceptible SP

7 Days Effective in Patients with CAP

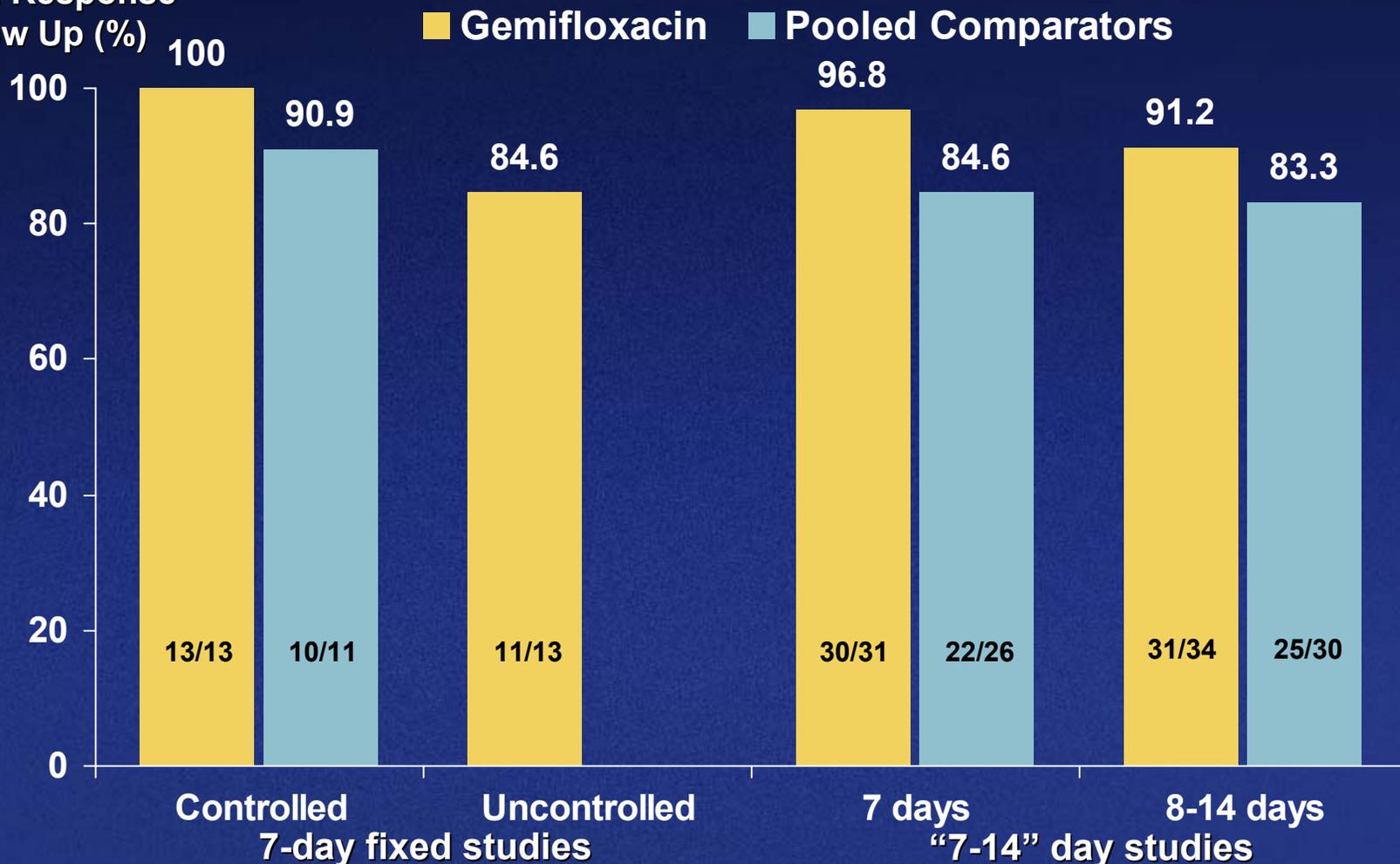
Clinical Response
at Follow Up (%)



FDA analysis of clinical response at follow-up by duration of therapy

Gemifloxacin 7 Days Effective in Patients with Severe CAP (Fine Criteria)

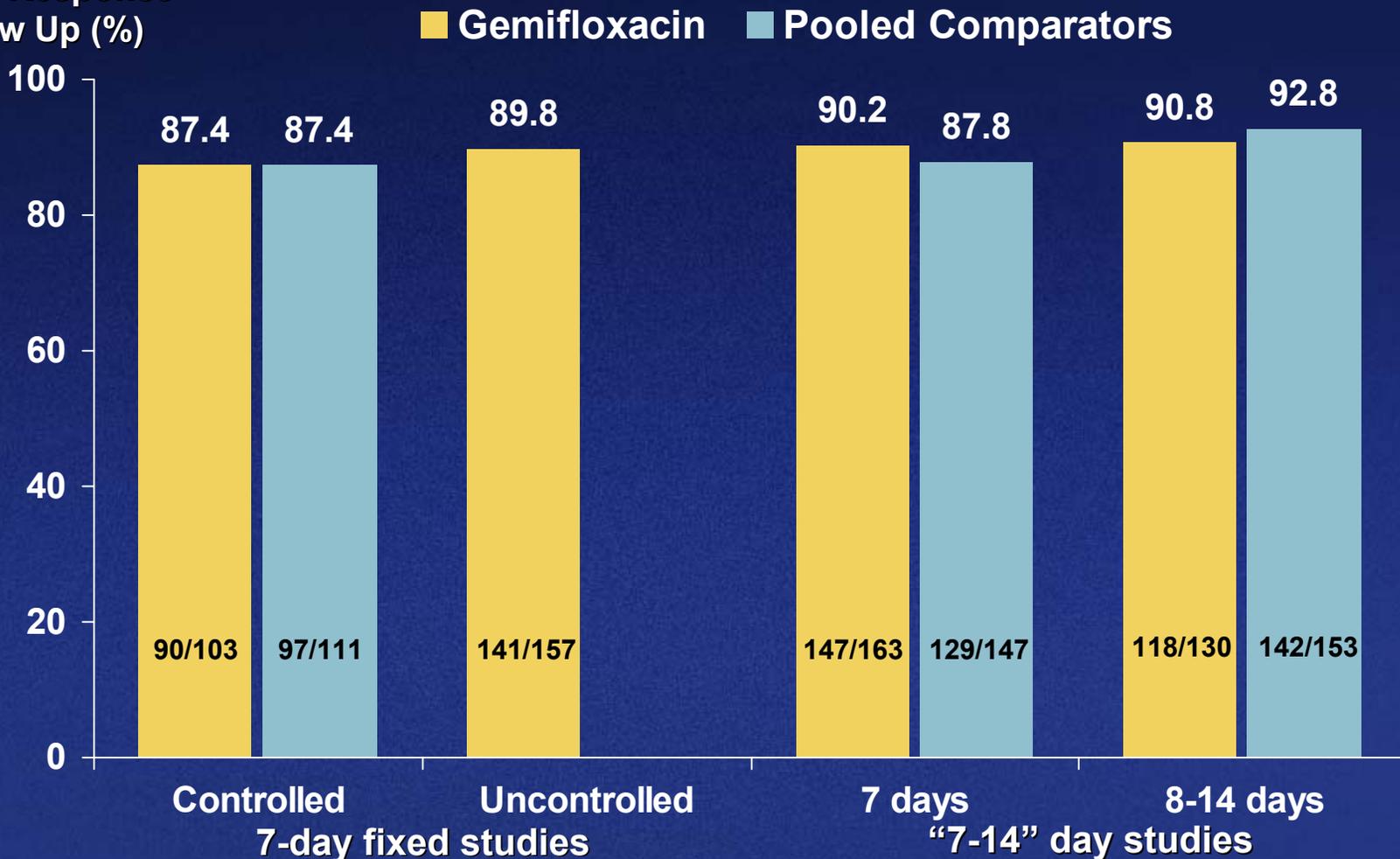
Clinical Response
at Follow Up (%)



FDA analysis of clinical response at follow-up for severe patients by duration of therapy

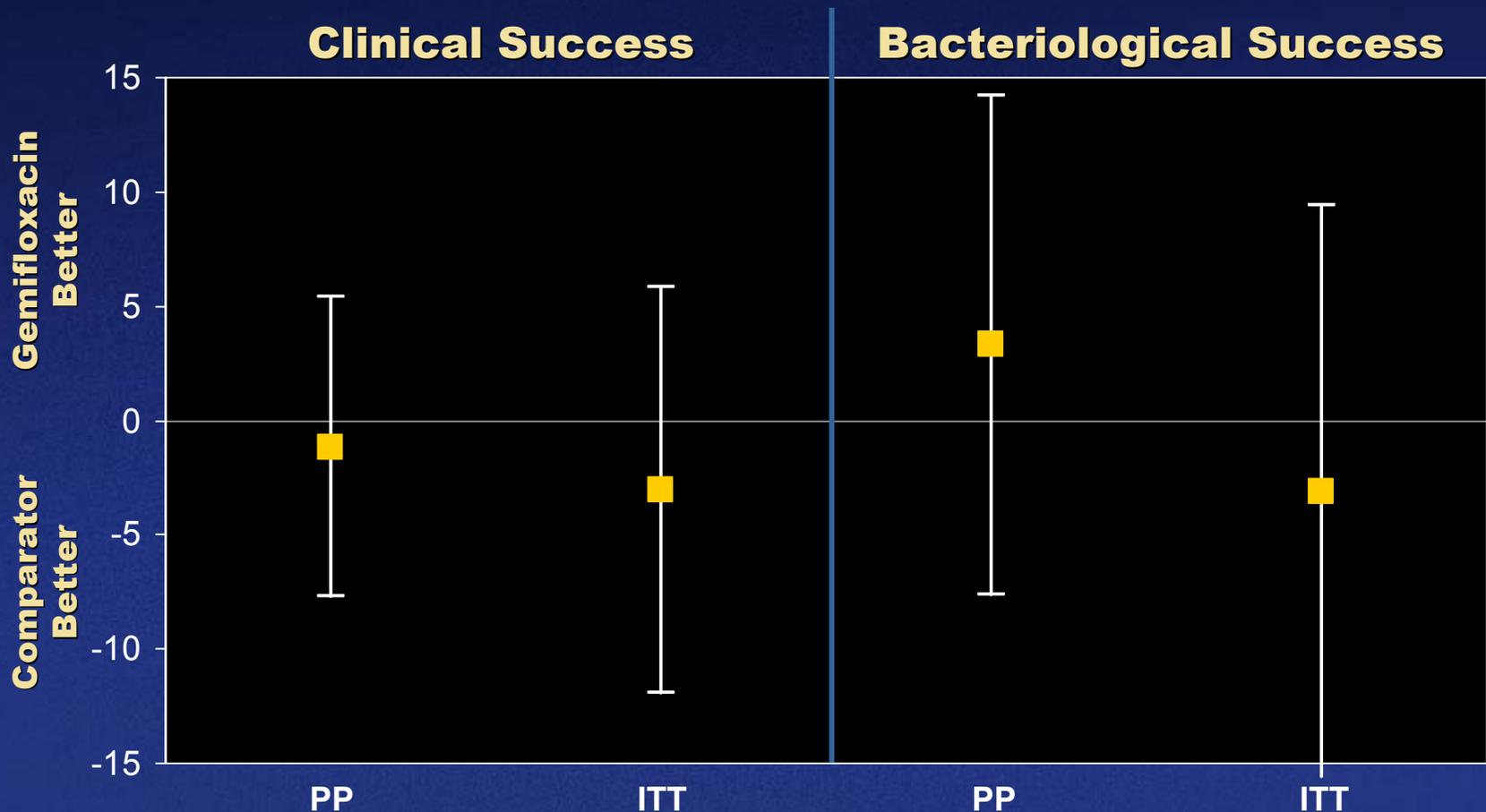
Gemifloxacin 7 Days Is Effective for Hospitalized Patients

Clinical Response at Follow Up (%)



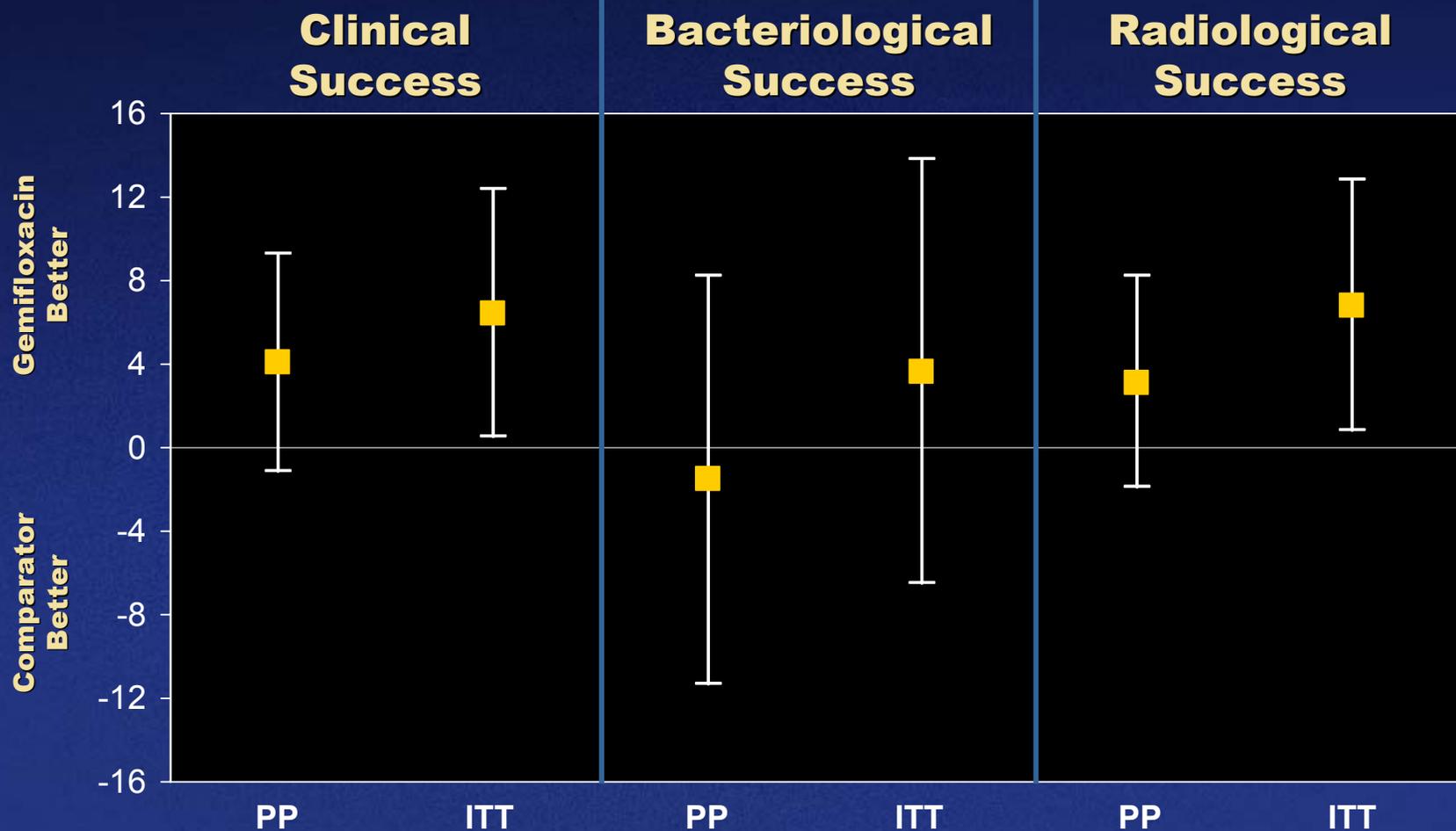
Oral Gemifloxacin as Effective as IV/PO Cephalosporin in Hospitalized Patients

Treatment Difference
at Follow-up (%; 95% CI)



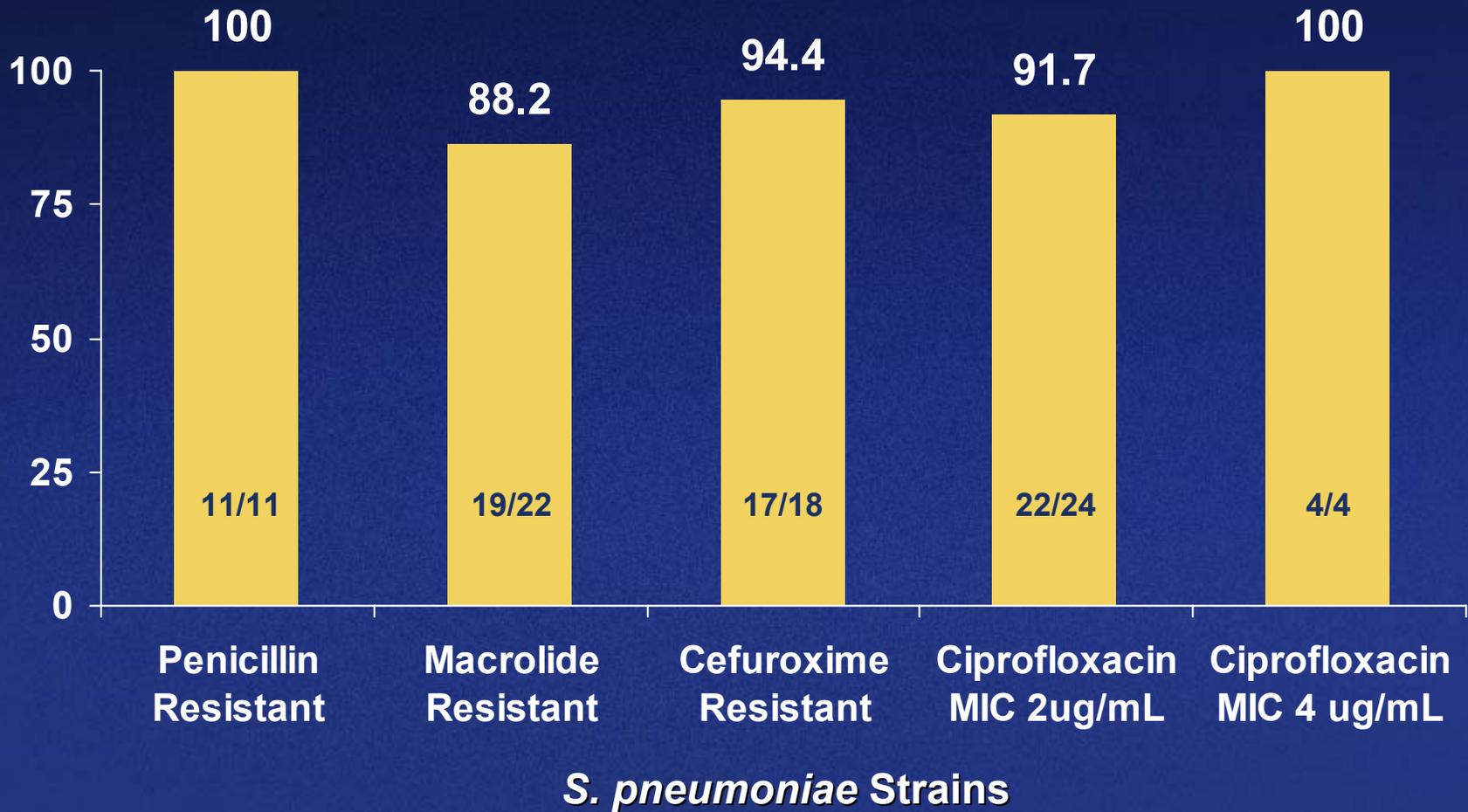
Gemifloxacin Statistically Superior to Potent Quinolone Trovafloxacin (Clinical & Radiological Response, ITT)

Treatment Difference
at Follow-up (%; 95% CI)



Gemifloxacin 7 Days Effective in Eradicating PRSP, MRSP, CRSP & Ciprofloxacin Non-susceptible SP

Clinical & Bacteriological
Response at Follow Up (%)



Conclusion

- AECB
 - Demonstrated clinical effectiveness
 - Faster bacteriological eradication
 - Reduced relapse rate
 - Reduced duration of hospitalization
 - Comparable to IV regimen
- CAP
 - Demonstrated clinical effectiveness
 - all severities
 - hospitalized patients
 - Comparable to IV regimen
 - Effective against PRSP, MRSP, CRSP & ciprofloxacin non-susceptible SP

Gemifloxacin – Safety Review

Gary Patou, MD
President, Genesoft Pharmaceuticals

Safety of Gemifloxacin

- Adverse events
- Serious adverse events
- Withdrawals
- Class effects
- Cutaneous manifestations

Gemifloxacin

Low Rate of Adverse Events (AEs)

Gemifloxacin

N = 6775

Pooled Comparators

N = 5248

	<i>n</i>	%	<i>n</i>	%
Diarrhea	343	5.1	325	6.2
Headache	304	4.5	273	5.2
Nausea	265	3.9	237	4.5
Rash	241	3.6	59	1.1
Abdominal pain	157	2.3	116	2.2
Vomiting	123	1.8	106	2.0
Dizziness	117	1.7	134	2.6
Rhinitis	105	1.5	74	1.4

Gemifloxacin

Few Serious AEs / Few Withdrawals Due to AEs

	Gemifloxacin N = 6775		Pooled Comparators N = 5248	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
Serious adverse experiences (SAE)	247	3.6	228	4.3
SAE of rash	7	0.1	1	<0.1
Withdrawal due to AE	264	3.9	226	4.3
Withdrawal due to treatment-related AE	152	2.2	109	2.1
Deaths	33	0.5	30	0.6

Quinolone Class Effects

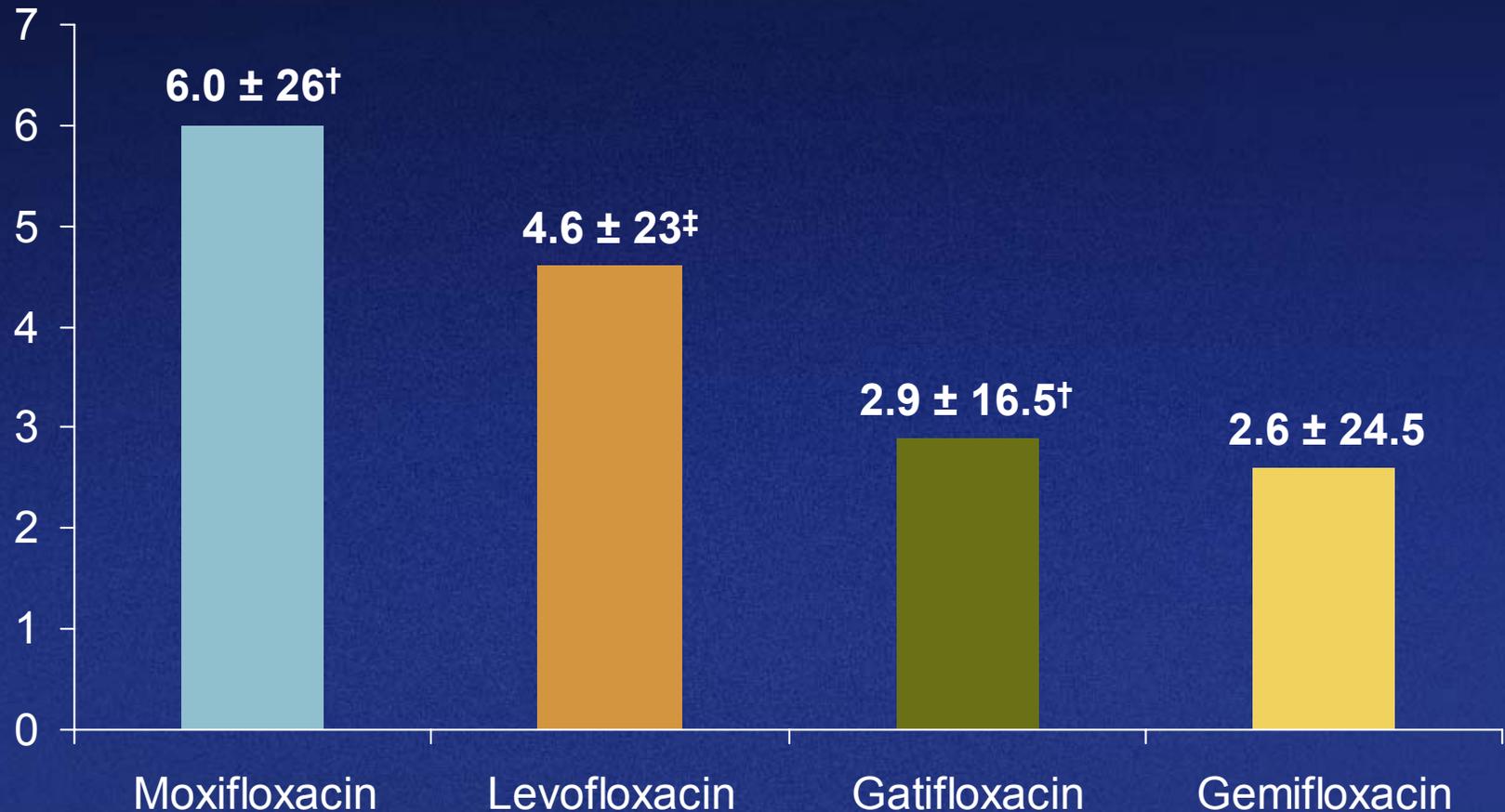
Gemifloxacin

Minimal Class Effects

- Antacid and sucralfate interactions only
- Low phototoxicity
- No dysregulation of glucose homeostasis

Effects on the QTc Interval

QTc prolongation (ms \pm SD)



Source: [†]Package insert, [‡]Iannini 500 mg, P J Antimicrob. Chemother. (2001) 47, 893

Hepatic Safety

Analyses

- Patients with pretreatment normal ALT
- Patients with pretreatment elevated ALT
- Patients reporting adverse events
 - Hepatic related AEs in patients with underlying liver disease
- Independent reviews
 - Paul Watkins, MD, University of North Carolina
 - James Lewis, MD, Georgetown University

Gemifloxacin 320 mg Elevated ALT Values on Therapy *Patients with Pretreatment Normal ALT Values*

Range	Gemifloxacin N=3989		All Comparators N=3588	
	<i>n</i>	%	<i>n</i>	%
<ULN	3800	95.3	3443	96.0
ULN-<2xULN	162	4.1	127	3.5
2 to <4xULN	26	0.7	15	0.4
4 to <6xULN	1	<0.1	2	<0.1
6 to <8xULN	0		0	
≥8xULN	0		1	<0.1

Gemifloxacin 640 mg Elevated ALT Values on Therapy *Patients with Pretreatment Normal ALT Values*

Range	Gemifloxacin N=592		Ciprofloxacin N=606	
	n	%	n	%
<ULN	569	96.1	600	99.0
ULN-<2xULN	14	2.4	6	1.0
2 to <4xULN	4	0.7	0	
4 to <6xULN	1	0.2	0	
6 to <8xULN	3	0.5	0	
≥8xULN	1	0.2	0	

Clinical Trial Signals Used to Predict Potential for Serious Hepatotoxicity

- Criteria for signals
 - “Hy’s rule (law)”
 - Hepatocellular jaundice (bilirubin \geq 3.0 mg/dL + very high serum ALT) due to drug administration
 - Eosinophilia associated with elevated ALT
- Database search parameters
 - Bilirubin \geq 1.5 mg/dL + ALT \geq 2x ULN
 - Cases further reviewed by expert hepatologists

No Treatment Emergent Signals for Serious Hepatotoxicity

	320 mg	640 mg
<ul style="list-style-type: none">• Signals<ul style="list-style-type: none">– Hy's rule– Eosinophilia + elevated ALT	0	0
<ul style="list-style-type: none">• Database search parameters<ul style="list-style-type: none">– Bilirubin \geq 1.5 mg/dL + ALT \geq 2x ULN	2	0

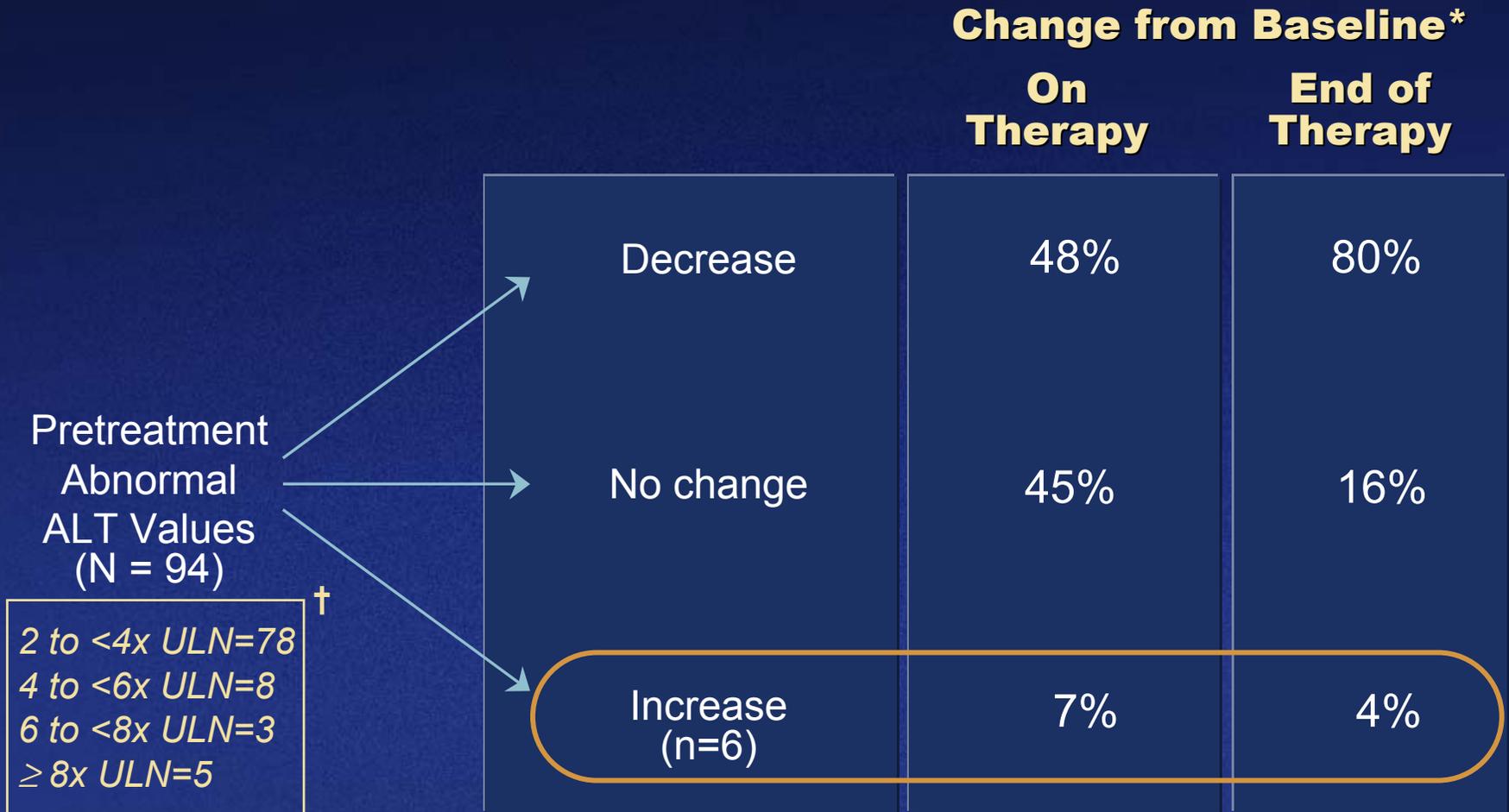
Elevated ALT Values on Therapy

Patients with Pretreatment Elevated ALT Values

Range	Gemifloxacin 320mg N=329		All Comparators N=255	
	n	%	n	%
<ULN	101	30.7	69	27.1
ULN-<2xULN	144	43.8	135	52.9
2 to <4xULN	67	20.4	44	17.3
4 to <6xULN	11	3.3	6	2.4
6 to <8xULN	3	0.9	1	0.4
≥8xULN	3	0.9	0	

Change in ALT Values at Either on Therapy or End of Therapy Visit

Patients with Pretreatment Elevated ALT Values



* Change to another range as shown in †

6 Patients with Further Increase in ALT on Treatment

Patients with Pretreatment Elevated ALT Values

Patient No	Lab Test	Pre-treatment	On Therapy	End of Therapy
11737	ALT	149	262	236
	Bilirubin	0.59	0.53	0.41
09311	ALT	122	151	279
	Bilirubin	0.65	0.53	0.65
05037	ALT	125	315	107
	Bilirubin	1.0	0.53	0.53
10594	ALT	185	211	342
	Bilirubin	1.0	0.65	0.59
10597	ALT	127	193	72
	Bilirubin	1.0	0.88	0.59
13830	ALT	110	501	132
	Bilirubin	0.59	0.59	0.47

No Hepatic AEs of Clinical Concern In Patients with Underlying Liver Disease

- AEs related to laboratory LFT abnormalities, not clinical findings
 - Patients were reviewed in extensive biochemical analyses previously described
 - None had symptoms of treatment-emergent hepatic disease
 - Withdrawal rate lower in gemifloxacin group (8%) vs. comparators (16%)

Hepatic SAEs

- Reported in 4 gemifloxacin treated subjects
- All from unblinded study 185
- All reported as laboratory LFT abnormalities
- All asymptomatic
- All reviewed in extensive biochemical analyses previously described
- None met criteria for Hy's rule

Summary

No Hepatic Safety Concern

- 320 mg dose devoid of defined signals predictive of serious hepatotoxicity potential
 - No subject met criteria for treatment-emergent Hy's rule
 - No signals of acute liver failure or irreversible injury
 - No evidence of hypersensitivity reaction
- 640 mg dose does not raise significant safety concerns about 320 mg dose
- No evidence that gemifloxacin treatment in patients with preexisting liver disease represents a liver safety concern

Gemifloxacin

Cutaneous Manifestations

Neil H. Shear, MD, FRCPC, FACP

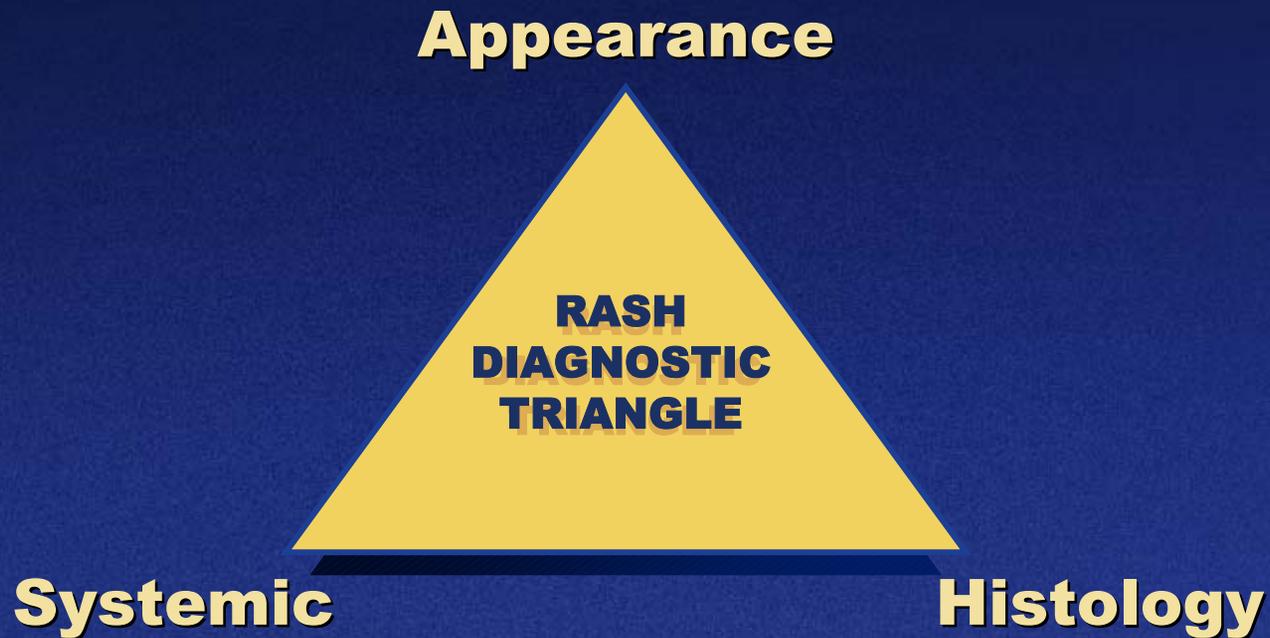
Professor and Chief Dermatology and Director,
Drug Safety Research Group, University of Toronto

Agenda

- Evaluation of drug rashes in general
- Observations of rash in gemifloxacin clinical trials
- Study 344 (done to characterize rash)
 - Landmark safety study
 - Enriched study population
 - Determined rash not an indicator of concern
- Interpretation of data
 - Higher rash rate vs. comparators
 - Observed rash is benign
 - Cross-reactivity rates are low



Rash Diagnostic Triangle



Drug-related Rashes – A Primer

Amoxicillin



Aspirin



Isoniazid



Tetracycline



Rash Morphology – A Primer

Exanthem



Urticarial



Pustular



Blistering



Rash Morphology – A Primer

Exanthem



Urticarial



Pustular



Blistering



+ Fever with systemic involvement =

**Hypersensitivity
Syndrome
Reaction
(HSR)**

**Serum
Sickness-
Like Reaction
(SSLR)**

**Acute
Generalized
Exanthematous
Pustulosis
(AGEP)**

**Stevens-
Johnson/
Toxic
Epidermal
Necrolysis
(SJS / TEN)**

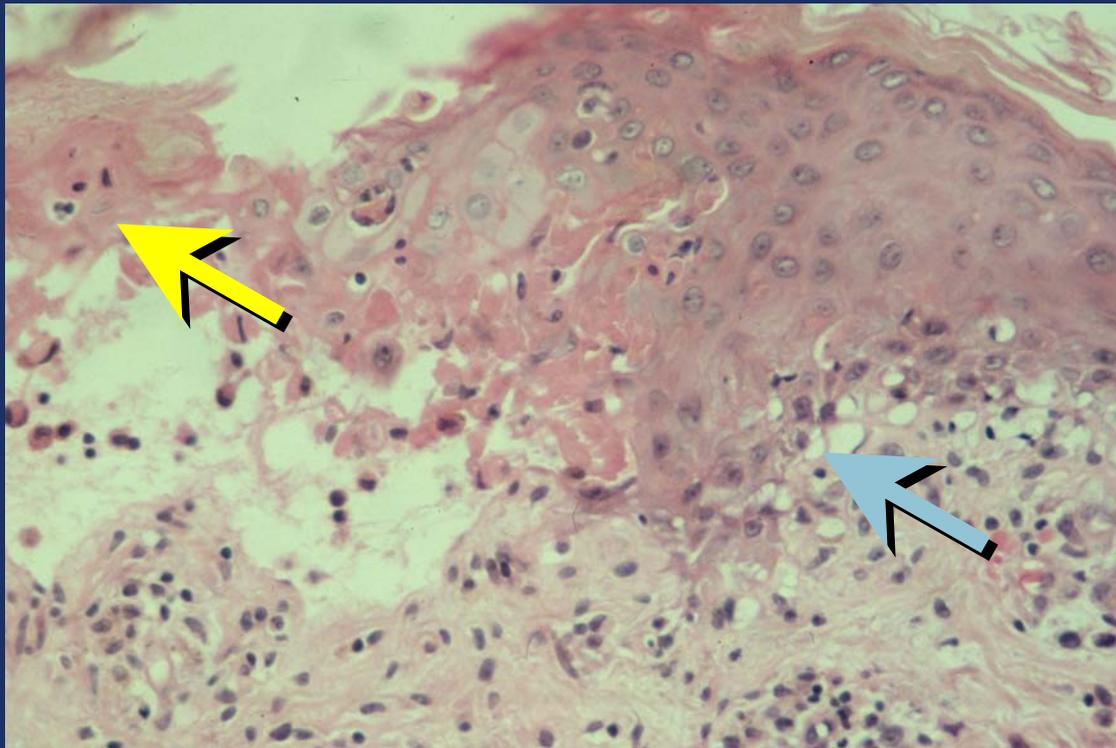
Important Cutaneous Drug Reactions – A Primer

- Angioedema
 - Swelling of face and lips
 - Hypotension
 - Wheezing
- Hypersensitivity syndrome reaction
 - Fever
 - Lymphadenopathy
 - Swollen face
- Stevens-Johnson syndrome / Toxic epidermal necrolysis
 - Cutaneous blistering
 - Hemorrhagic crusting of mucosa

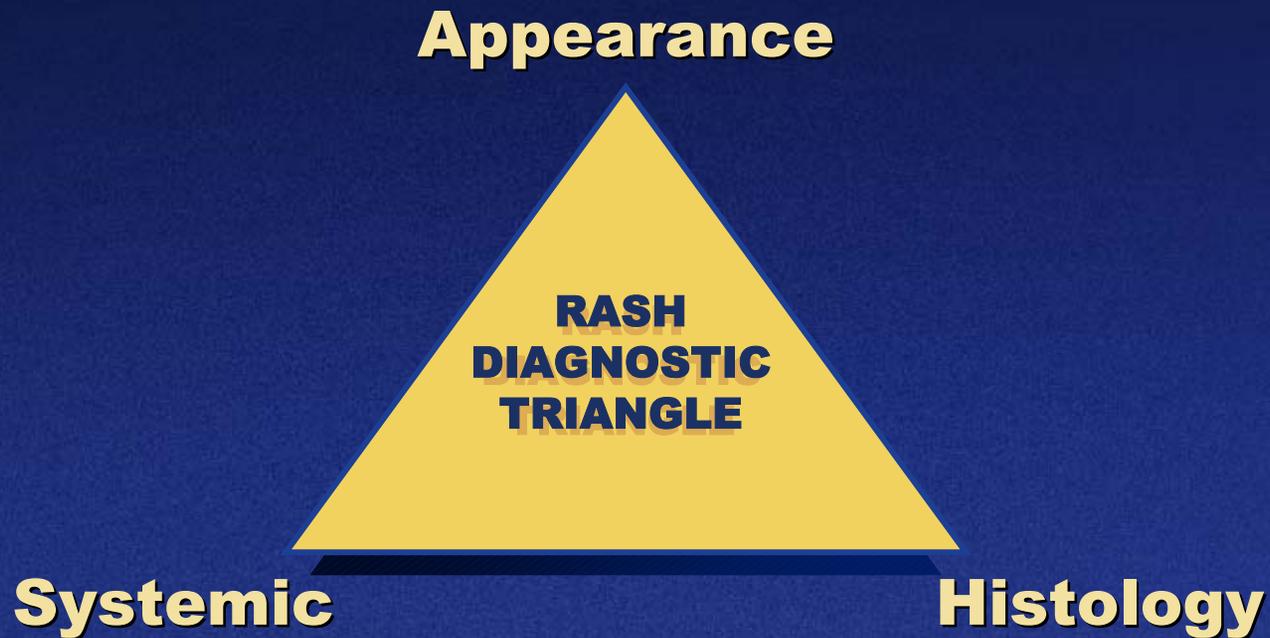
Relationship of Hypersensitivity Syndrome Reaction (HSR) to SJS / TEN

- Pathogenesis for HSR and SJS / TEN
 - Shared for many drugs (cotrimoxazole, phenytoin, carbamazepine, lamotrigine)
 - Predominant CD8+ cell infiltrate in skin
- HSR for phenytoin & carbamazepine is 1/3000
- SJS / TEN incidence for phenytoin & carbamazepine is 1/10000
- HSR is a potential harbinger of SJS / TEN

Histology of Stevens-Johnson / TEN



Rash Diagnostic Triangle



Rash Characteristics in Clinical Trials

	Gemifloxacin N = 6775	Pooled Comparators N = 5248
Prevalence	3.6 %	1.1 %
Median onset	9 days	4 days
Median duration	5 days	4 days
Longest duration	> 30 days	> 30 days
Withdrawals due to rash	0.9 %	0.3 %
Cutaneous SAEs	0.1%	< 0.1 %
Severity: Mild/Moderate/Severe	1.8 / 1.3 / 0.5%	0.6 / 0.4 / 0.1%

7 Rash SAEs in Gemifloxacin Clinical Trials (N=6775)

Patient Description	Center Location	Reason for Seriousness	Comments
<ul style="list-style-type: none"> ▶ 18 yr male ▶ 7days dosing ▶ ABS 	Hungary	Hospitalization	Tested positive for mono: “Rash probably associated with underlying mononucleosis and drug.”
<ul style="list-style-type: none"> ▶ 24 yr female ▶ 8 days dosing ▶ ABS 	Poland	Hospitalization	Treated with steroid and antihistamine. Recovered by day three.
<ul style="list-style-type: none"> ▶ 52 yr female ▶ 9 days dosing ▶ ABS 	Poland	Hospitalization	Mild rash. No medical reason for hospitalization but patient required reassurance.
<ul style="list-style-type: none"> ▶ 60 yr female ▶ 8 days after 1st dose ▶ UTI 	Poland	Hospitalization	Treated with steroid, antihistamine and calcium. Recovered within 7 days.

ABS = acute bacterial sinusitis, UTI = urinary tract infection

7 Rash SAEs in Gemifloxacin Clinical Trials (N=6775) - Cont.

Patient Description	Center Location	Reason for Seriousness	Comments
<ul style="list-style-type: none"> ▶ 87 yr male ▶ 7 days dosing ▶ CAP 	Canada	Investigator judgment	Rash 48 hours post therapy; asymptomatic, afebrile. Rash began fading in 2 days without intervention.
<ul style="list-style-type: none"> ▶ 72 yr male ▶ 2 days dosing ▶ AECB 	Netherlands	Investigator judgment	Allergic to gold and penicillin. Receiving 8 co-medications. Treated with antihistamine. Rash resolving at day 18.
<ul style="list-style-type: none"> ▶ 42 yr female ▶ 4 days dosing ▶ ABS 	USA	Investigator judgment	Serum Sickness. Onset 13 days after last dose. CXR infiltrate in RLL, serological diagnosis of acute mycoplasma pneumoniae infection. Largely resolved after 15 days.

Quinolone Rechallenge Data

	Total Exposed	Number Reporting Rash On Rechallenge
Previous exposure to another quinolone	181	3
Previous exposure to gemifloxacin with no rash	41	0
Subsequent exposure to another quinolone after gemifloxacin rash	11	0

Frequency Distributions of Rash

**Gemifloxacin
N = 6775**

**Pooled
Comparators
N = 5248**

		%	%
Gender	Males	2.4%	0.8%
	Females	4.7%	1.4%
Age	<40 yrs	6.7%	1.3%
	≥40 yrs	2.5%	1.1%
Planned Treatment Duration	5 days	1.2%	0.9%
	7 days	5.3%	1.1%
	10 days	6.4%	1.1%
	14 days	7.4%	2.9%

Highest Risk Group

Women <40 yr Treated for >7 Days

Rash rate in women < 40
treated for 10 days

- Gemifloxacin
- Comparators

15.3%

1.9%

Objectives for Phase I Dermatology Safety Study

**To assess, in an enriched population,
with extended dosing:**

- Clinical and histological features of drug rash
- Cross-sensitization potential with ciprofloxacin
- Sub-clinical sensitization potential
- Potential relationship between plasma levels of gemifloxacin, *N*-acetyl gemifloxacin and rash

Study Design

PART A

Females 18-40 Yrs

(5:1)

10 days gemifloxacin
320mg daily

10 days ciprofloxacin
500mg bid

Rash

No Rash

Rash

No Rash

Study Design

PART A

Females 18-40 Yrs

(5:1)

10 days gemifloxacin
320mg daily

10 days ciprofloxacin
500mg bid

Rash

No Rash

Rash

No Rash

4-6 week
wash-out period

PART B

(3:1)

(1:1)

ciprofloxacin

placebo

gemifloxacin

placebo

placebo

ciprofloxacin

Cross-
sensitization
potential

Sub-Clinical
sensitization
potential

Baseline

Key Evaluation Criteria

- Skin
 - Board-certified dermatologist examined clinical rash within 24 hrs
 - Rash photographed
 - 3 biopsies from rash and 3 from non-rash sites
- Blood and urine sampling
 - Drug levels
 - Clinical chemistry including liver function tests
 - Standard hematology including eosinophils
 - EBV screen
- 12 Lead ECG taken pre dose and 2 hrs post dose Day 1

Histology, Pharmacokinetics and Photographic Data

- Histology review
 - 288 subjects biopsied from parts A and B
 - 576 histology slides
 - 2,880 immunofluorescence slides
 - IgG, A, M and C3 plus negative and positive controls
 - 4,032 immunohistochemistry slides
- Population pharmacokinetic analysis
 - 7943 gemifloxacin plasma concentration-time data
 - 7934 *N*-acetyl gemifloxacin plasma concentration-time data
- Photographic data
 - 300 subjects with photographic records

Outcome for Part A

PART A

Females 18-40 Yrs

(5:1)

10 days gemifloxacin
320mg daily

10 days ciprofloxacin
500mg bid

Rash

No Rash

Rash

No Rash

(%) with rash 260 (31.7)

7 (4.3)

4-6 week
wash-out period

PART B

(3:1)

(1:1)

ciprofloxacin

placebo

gemifloxacin

placebo

placebo

ciprofloxacin

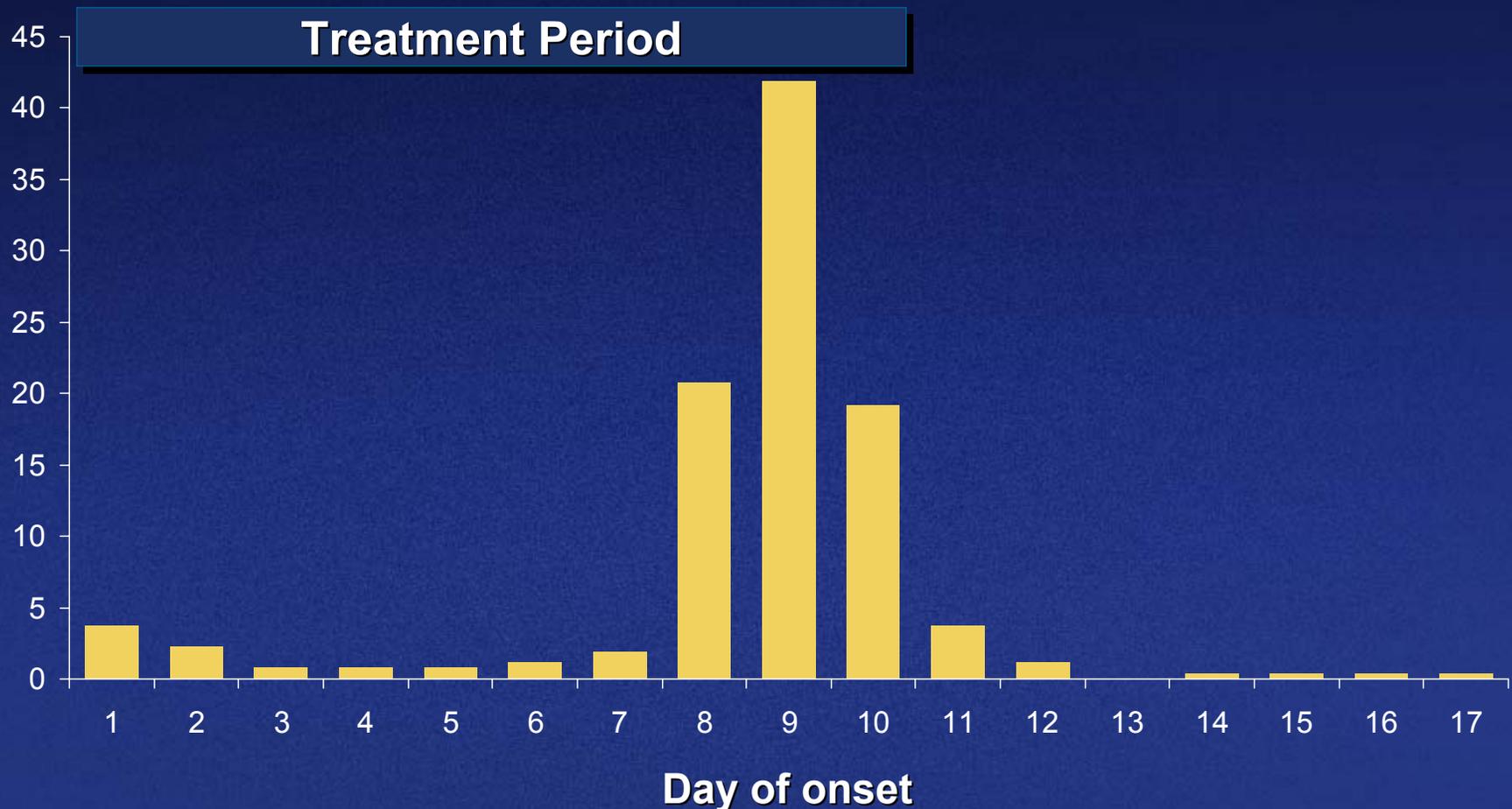
Cross-
sensitization
potential

Sub-Clinical
sensitization
potential

Baseline

Majority of Rashes Occur Days 8-10

% of Subjects with Rash (N = 260)



RASH
DIAGNOSTIC
TRIANGLE

Systemic

Histology

Rash Morphology



Average



Worst

Reported Cases of Severe Rash



Reported Cases of Severe Rash



Reported Cases of Severe Rash



Reported Cases of Severe Rash



Reported Cases of Severe Rash





No Angioedema

Sign Or Symptom	Patients		Comments
	<i>n</i>	%	
"Urticaria"	25	9.6%	Time of onset and duration similar to other rashes; biopsy findings similar to non urticarial subjects
Facial edema	11	4.2%	All but two had maculopapular rash on face. With 2 exceptions (one subject urticaria and another with diarrhea) none had any other symptoms indicating a type I reaction

No SJS/TEN

No Hypersensitivity Syndrome

Appearance

STUDY
344

RASH
DIAGNOSTIC
TRIANGLE

Systemic

Histology

Sign Or Symptom	Patients		Comments
	<i>n</i>	%	
Mucosal involvement	15	5.8%	Dry mouth or eyes, macular erythema on lips and aphthous buccal ulcers, <u>no</u> hemorrhagic blistering
Wheezing	1	0.4%	No other symptoms possibly indicating a Type I reaction
Fever with rash	6	2.3%	One associated with lymphadenopathy; none associated with other systemic symptoms

No Other Markers of Systemic Involvement



- No clinically significant rise in serum transaminases and no association with rash

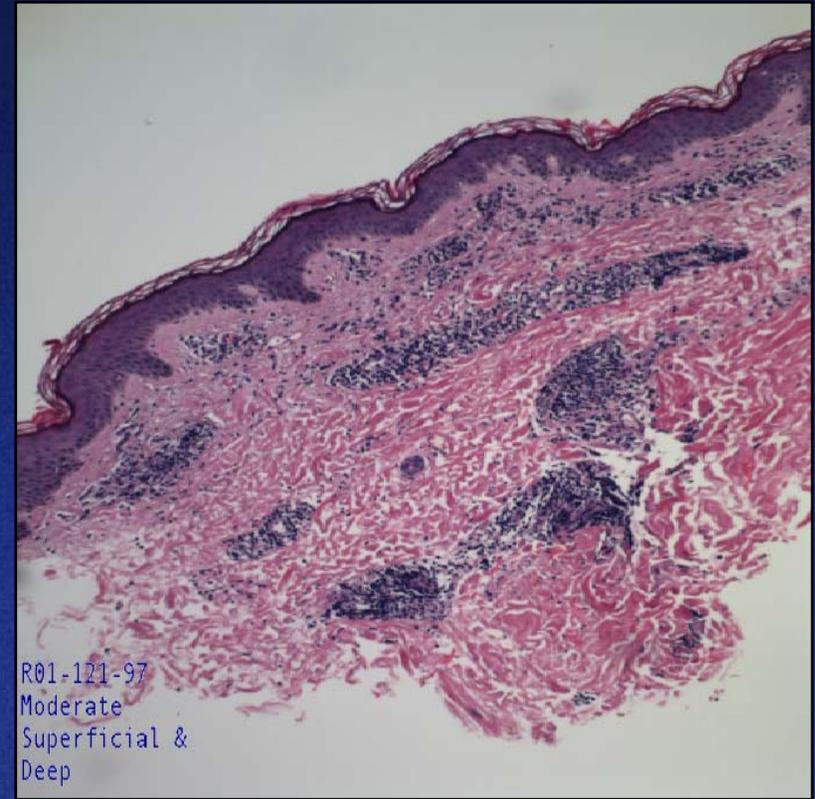
	Rash N=260	No Rash N=559
ALT	0	0
Alk Phos	0	0
AST	0	2 (0.4%)
Total Bilirubin	2 (0.8%)	4 (0.7%)
GGT	0	0

- No significant changes in eosinophil counts

Histopathology



Slide R01 128-14 :
Mild lymphocytic infiltrate
278 of 288



Slide R01 121-97 :
Moderate superficial & deep infiltrate
10 of 288

Pathology Consistent with Mild Exanthematous Eruption



- Mild superficial perivascular lymphocytic infiltrate
- 10 biopsies showed a denser infiltrate
- Inflammatory infiltrate was composed of lymphocytes
- Mixed CD4 and CD8 population
- No erythema multiforme
- No epidermal necrosis
- No vasculitis

Evaluation of Sensitization Potential

PART A

Females 18-40 Yrs

10 days gemifloxacin
320mg daily

10 days ciprofloxacin
500mg bid

Rash

No Rash

Rash

No Rash

(5:1)

4-6 week
wash-out period

PART B

(3:1)

(1:1)

ciprofloxacin

placebo

gemifloxacin

placebo

placebo

ciprofloxacin

with rash 15 (8) 2 (1) 8 (6) 7 (5) 0 7 (5)

% with rash 10.4%
(5.9%) 3.9%
(2.0%) 3.2%
(2.4%) 2.7%
(2.0%) 4.9%
(3.5%)

Cross Sensitization Potential

PART A

Females 18-40 Yrs

10 days gemifloxacin
320mg daily

Rash

4-6 week
wash-out period

PART B

(3:1)

ciprofloxacin

placebo

with rash 15 (8) 2 (1)

% with rash 10.4% (5.9%) 3.9% (2.0%)

Sub-clinical Sensitization Potential

PART A

Females 18-40 Yrs

10 days gemifloxacin
320mg daily

No Rash

4-6 week
wash-out period

PART B

(1:1)

gemifloxacin

placebo

with rash

8 (6)

7 (5)

% with rash

3.2%
(2.4%)

2.7%
(2.0%)

Evaluation of Sensitization Potential

PART A

Females 18-40 Yrs

10 days ciprofloxacin
500mg bid

Rash

No Rash

4-6 week
wash-out period

PART B

placebo

ciprofloxacin

with rash

0

7 (5)

% with rash

4.9%
(3.5%)

Part B Summary

- Low cross-sensitization
- No evidence of sub-clinical sensitization
- Rashes in Part B tended to be
 - earlier onset
 - shorter duration
 - mild
 - affecting <10% of body surface area
 - similar to ciprofloxacin associated rash in Part A

Summary Study 344

- 10 day exposure in women under age 40
- Rash rate of 31.7%
- No cases of hypersensitivity syndrome
 - 1 case of fever and lymphadenopathy
- No cases of SJS / TEN
 - 1 case of buccal aphthae
- Rash was clinically and pathologically an exanthem

Summary Patient Trial Data

- Rate of rash in 6775 subjects was 3.6% overall
- Rate of rash in women under 40, using 10 days of treatment was 15.3%
- 1 case suggestive of serum sickness-like reaction
- No angioedema
- No Stevens-Johnson / TEN
- No hypersensitivity syndrome

Interpretation

Gemifloxacin Associated Rash

- Rash Rate = **3.6%** in overall patient population
- Highest risk group identified as women under 40
- The observed rash is **benign** by multiple measures
- Well characterized in landmark drug rash safety study
- No HSR or SJS / TEN in ~10,000 exposures at all doses
- Low sensitization potential

Gemifloxacin Safety Summary

- No liver or clinically significant QTc problems
- Rash rate in CAP (4.7%) and AECB (1.5%) greater than controls but:
 - No evidence of significant morbidity
 - Low rate of cross sensitization
 - No sub-clinical sensitization

Gemifloxacin Benefit/Risk

Current AECSB & CAP Treatment Choices

- Antibiotic resistance \Rightarrow dependence on newer fluoroquinolones
- Increasing fluoroquinolone resistance
- Limitations of current fluoroquinolones
 - Gatifloxacin “life threatening hyperosmolar coma” †
 - Moxifloxacin “QTc prolongation warning” †
 - Levofloxacin “pneumococcal pneumonia treatment failure” ‡
- Gemifloxacin can help fill unmet medical need

Gemifloxacin Benefit/Risk

- Potent, with favorable PK/PD
 - Shorter therapy courses
 - Less resistance pressure
- Active against resistant (including quinolone-resistant) organisms
 - Effective empiric treatment choice
- Beneficial beyond acute treatment period
 - Reduced AECB relapse rates
 - Reduced duration of hospitalization

Gemifloxacin Benefit/Risk

- High oral bioavailability
 - As effective orally as IV/oral switch comparator regimens in AECB & CAP
- No significant drug-drug interactions
 - CAP & AECB comprised of large numbers of elderly patients, many on co-medications
- Both renal and biliary clearance
 - No dosage adjustment in hepatic or mild-to-moderate renal impairment

Gemifloxacin Benefit/Risk

- Good AE profile
- Well tolerated/low withdrawal rates
- Quinolone class effects
 - No hepatic safety signal
 - Short QTc prolongation (2.6 msec)
- Overall rash rate 3.6%
- Rash characteristics
 - Typical mild drug rash
 - Rate higher in sub-population
 - No evidence of significant morbidity
 - Low sensitization potential

Gemifloxacin Risk Management

- Target label population (AECB and CAP patients) predominantly over 40 years old
- Short treatment course minimizes incidence of rash
- Fixed dosage packs: 5 or 7 days only
- Clinical program including study 344 demonstrates that rash is clinically manageable
- Adverse experiences described in package insert
- Physician education
- Active pharmacovigilance Phase IV study

Conclusions

- ***Gemifloxacin in AECB and CAP is a critically needed addition to physicians' armamentarium***

Odds ratios and 95% Confidence Intervals for the Effects of OC Use in the Model Containing Planned Duration of therapy, Age and Country group as Explanatory Variables

Explanatory Variable	Value	Odds Ratio (95% CI)	Likelihood Ratio Test		
			DF	Chi-squared	P-value
OC use*	Yes	1.491 (0.892 – 2.492)	1	2.30	0.13
	No	1.000			

* results obtained from model using only females who were younger than 40 years

Odds ratios and 95% confidence intervals for the effects of HRT use in the model containing planned duration of therapy, age and country group as explanatory variables

Explanatory Variable	Value	Odds Ratio (95% CI)	Likelihood Ratio Test		
			DF	Chi-squared	P-value
HRT use*	Yes	1.900 (1.122 – 3.217)	1	5.36	0.021
	No	1.000			

* results obtained from model using only females who were younger than 40 years

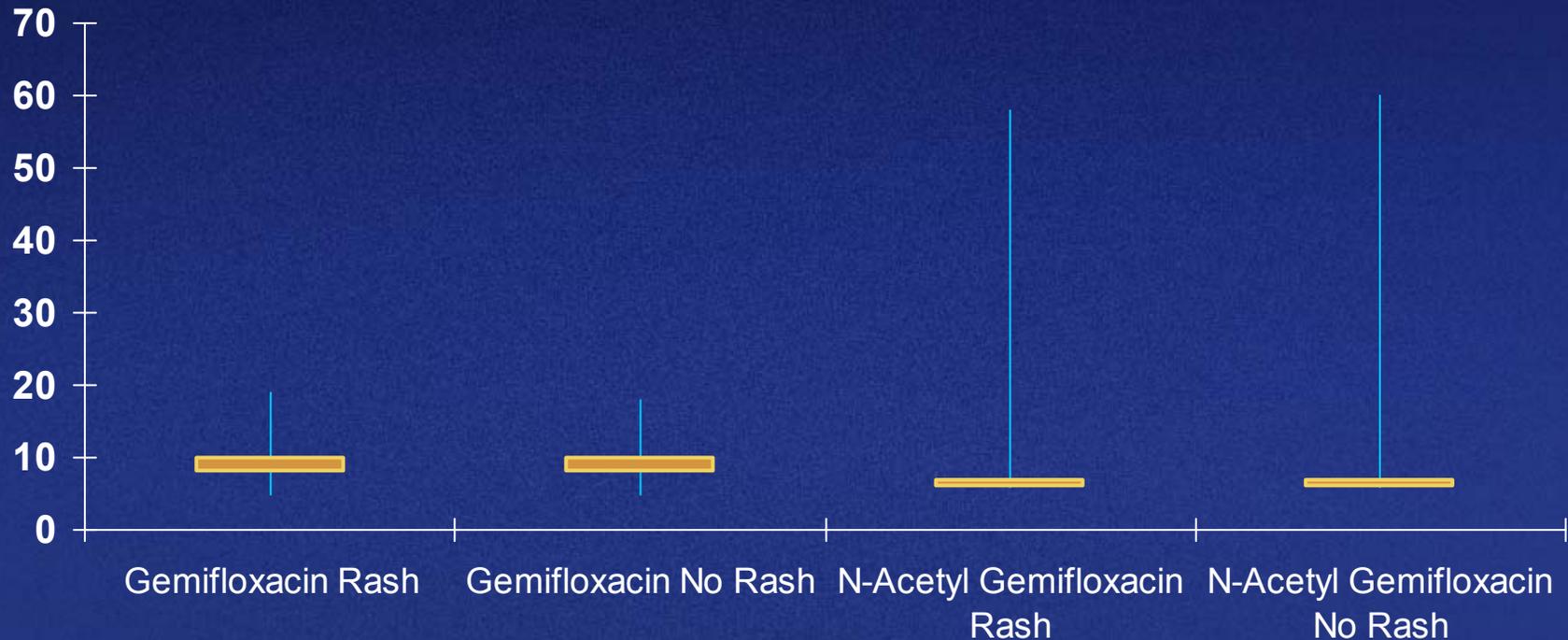
Demographic Characteristics of Study Population

Parameter	Age (years)	Weight (kg)	Height (m)	Race	Skin Type
N	1011	1011	1011	White: 929	I: 76
Mean	28	64.4	165.7	Black: 2	II: 218
SD	6.2	9.0	6.9	Other: 11	
Range	18–40	44.8–96.6	141.0–187.0	Oriental: 20	III: 478
				Hispanic: 49	IV: 239

Rash Not Related to Drug Levels

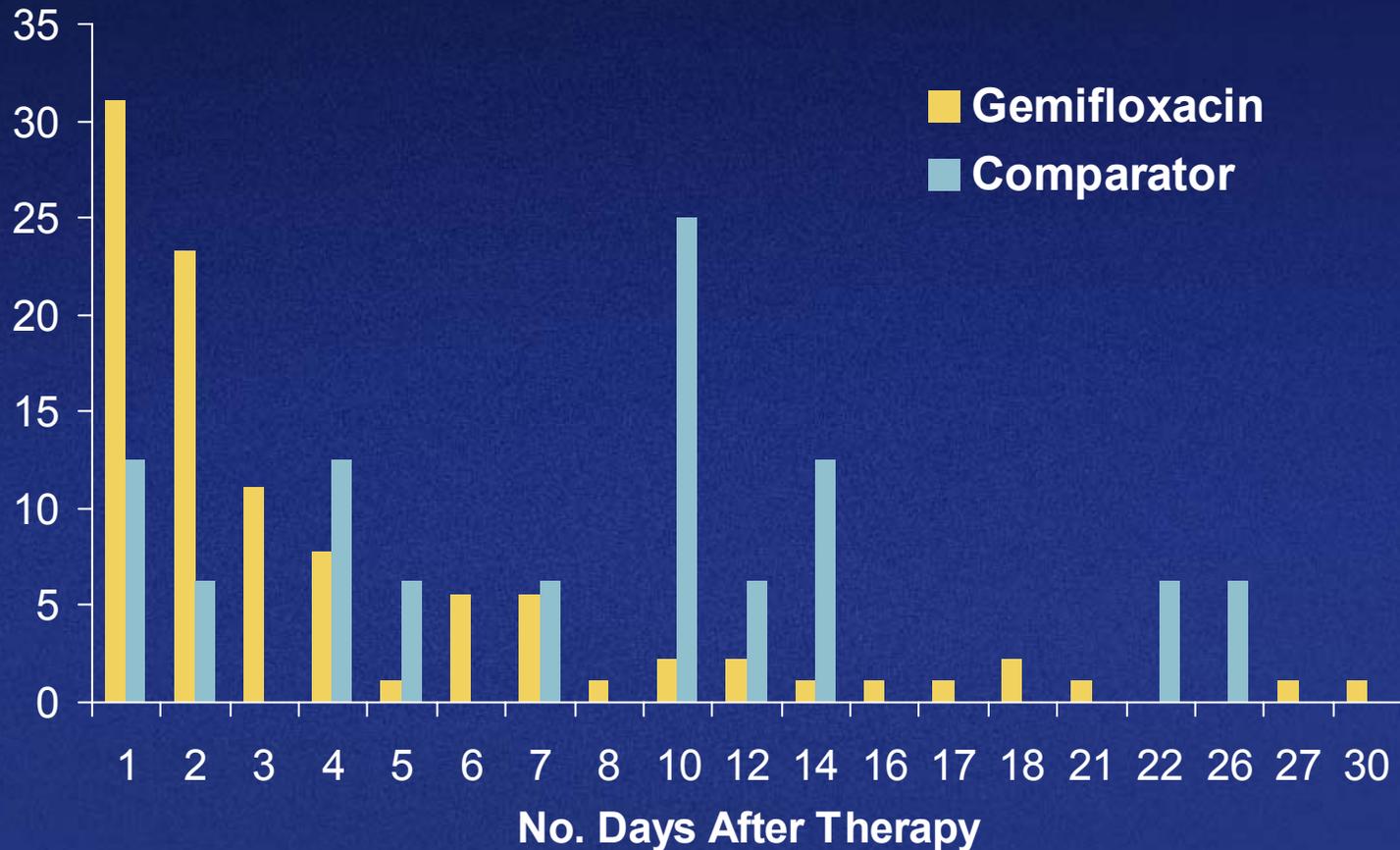
- No relationship between serum concentrations of gemifloxacin or its N-acetyl metabolite and occurrence of rash

AUC ($\mu\text{g}\cdot\text{h}/\text{mL}$)



Number of Days After Therapy When Rash Started *Clinical Trial Population*

% of Patients with
Rash after Therapy



Study 139 – Clinical & Smoking History (ITT)

Clinical/Smoking History	Treatment Group	
	Gemifloxacin 320mg od N=214	Clarithromycin 500mg bid N=224
Duration of Chronic Bronchitis (year)		
n	213	224
Mean (SD)	12.7 (12.1)	12.4 (11.4)
Range	2.0 – 65.1	1.8 – 66.2
Number of Exacerbations Treated with Antibacterials in Last Year, n(%)		
0	41 (19.2)	40 (17.9)
1 to 4	143 (66.8)	158 (70.5)
> 4	29 (13.6)	26 (11.6)
Unknown	1 (0.5)	0
Use of Supplemental Oxygen, n(%)		
Yes	21 (9.8)	14 (6.3)
Use of Systemic Steroids in Last Year, n(%)		
Yes	54 (25.2)	55 (24.6)
Number of Pack Years Patient Has Smoked		
0	34 (15.9)	40 (17.9)
>0 to 30	88 (41.1)	86 (38.4)
>30	91 (42.5)	98 (43.8)
Unknown	1 (0.5)	0
Smoked in Last Month, n(%)		
Yes	95 (44.4)	107 (47.8)

Efficacy of Gemifloxacin, Moxifloxacin and Gatifloxacin Against *S. pneumoniae* in the Rat RTI Model

<i>S. pneumoniae</i> strain	MIC ($\mu\text{g/mL}$)			Log ₁₀ CFU/lungs			
	GEMI	MOXI	GATI	GEMI	MOXI	GATI	NTC
404053	≤ 0.03	0.06	0.125	≤ 1.7	≤ 1.7	≤ 1.7	6.5 ± 1.5
406081	≤ 0.03	0.125	0.25	≤ 1.7	≤ 1.7	≤ 1.7	6.8 ± 1.0
205118	≤ 0.03	0.25	1.0	$1.9 \pm 0.6^{*,**}$	2.9 ± 1.6	3.7 ± 1.1	6.3 ± 1.1
305313	0.125	2.0	4.0	4.0 ± 0.8	3.5 ± 1.4	4.1 ± 1.4	6.1 ± 1.5
509063	0.25	2.0	4.0	$3.8 \pm 1.6^*$	4.6 ± 1.3	6.1 ± 1.2^c	7.0 ± 0.4
PT 9424123	0.25	2.0	4.0	3.1 ± 0.7	3.6 ± 1.9	4.0 ± 1.4	6.8 ± 1.4
622286	0.125	1.0	1.0	$2.6 \pm 1.2^{**}$	4.6 ± 2.0	3.6 ± 2.3	7.4 ± 1.4
402123	0.25	2.0	4.0	3.6 ± 1.1	3.9 ± 1.3	3.1 ± 1.1	6.1 ± 2.2

Genetically-defined second step mutants

* significantly different compared with GATI $p < 0.05$, ** significantly different to MOXI $p < 0.05$

^c Not significantly different to non-treated controls (NTC) $p > 0.05$